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ABSTRACT

This volume articulates a general program of implementation strategies and provides practical advice for integrating environmental medicine content into medical education. Chapter 1 is an introduction to the issues and the organization of the volume. Chapter 2 lays the foundation for a curriculum centered on six competency-based learning objectives. Chapter 3 uses these objectives as a framework for identifying likely access points in the curriculum for integrating environmental medicine into today's medical studies. Chapter 4 addresses both the barriers to implementing such a curriculum and the opportunities for reducing these barriers. Chapter 5 presents concluding remarks that summarize some of the events that led to the report. Recommendations for integrating an enhanced program of environmental medicine throughout the system of medical education and practice appear at the ends of chapters 2 through 4. Four extensive appendixes which comprise most of the document contain resources including: an example of a tool for teaching how to elicit a good environmental history; a paper on the relevance of and opportunities for integrating environmental medicine into common medical school courses and rotations; 55 case studies useful in teaching and learning; a list of agencies, organizations, services, references (books, reports, and curriculum resources) and tables of environmental health hazards. (Contains 66 references.) (JB)

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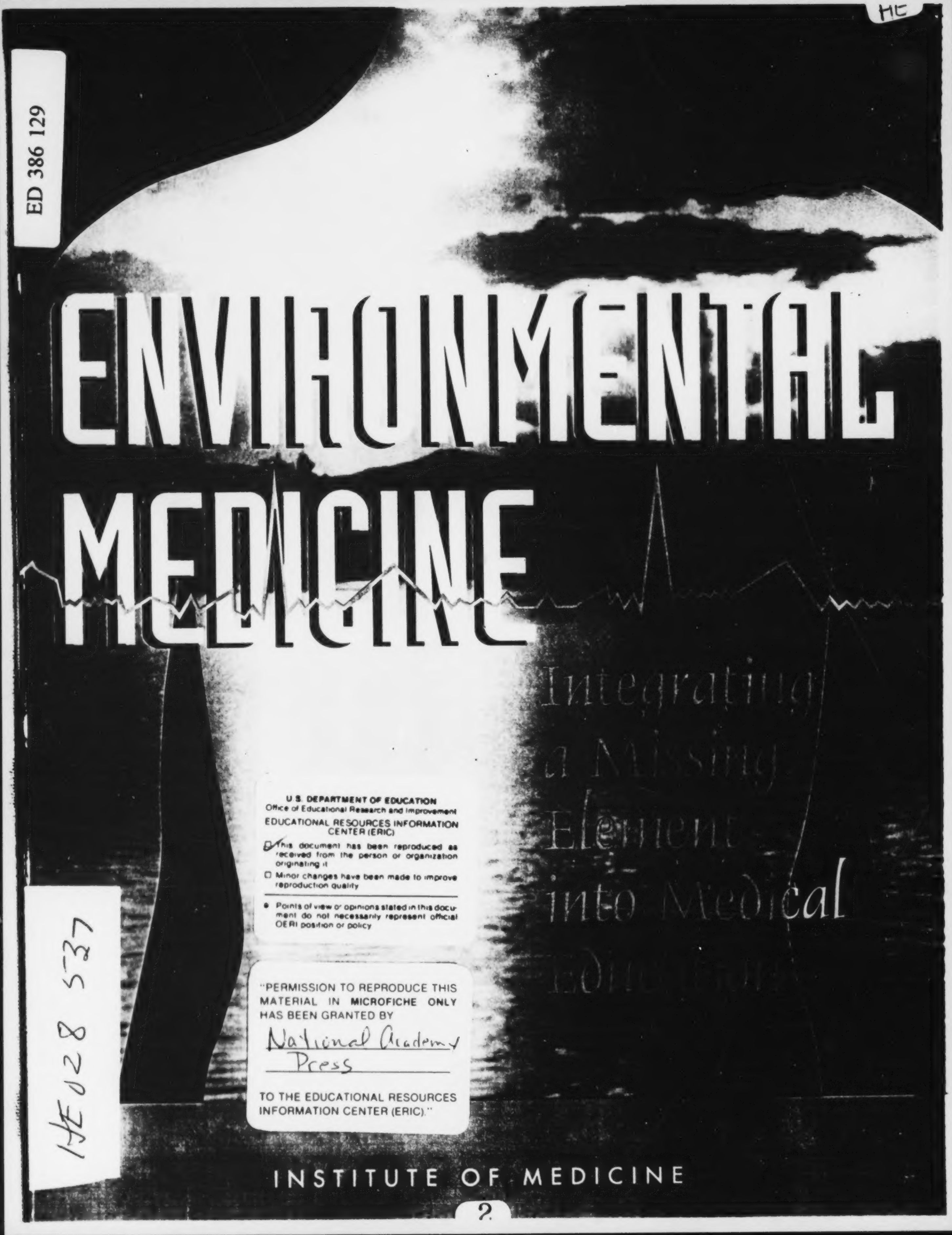

ENVIRONMENTAL MEDICINE

Integrating a Missing Element into Medical Education

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ENVIRONMENTAL MEDICINE

Integrating a Missing Element into Medical Education

Andrew M. Pope and David P. Rall, Editors

Committee on Curriculum Development in Environmental Medicine

Division of Health Promotion and Disease Prevention

INSTITUTE OF MEDICINE

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The image adopted as a logotype by the Institute of Medicine is based on a relief carving from ancient Greece, now held by the Staatlichemuseen in Berlin.

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*Appointment ended September 1, 1994.

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Preface

In its broadest sense, the environment is one of the major determinants of human health and well-being. Healthy environments promote individual and community health; unhealthy environments can create substantial morbidity, mortality, and disability, in addition to sapping the economic welfare of societies. In a previous report, produced by the Committee on the Role of the Primary Care Physician in Occupational and Environmental Medicine, the Institute of Medicine (IOM) called on primary care physicians to enhance their roles in occupational and environmental medicine, noting that these providers often serve as the point of first contact for persons with work- and environment-related health problems or risks (Institute of Medicine, 1988). At the same time, IOM found that the training of primary care physicians in occupational and environmental medicine is lacking at all levels of medical education.

The present report continues and expands upon the work of the previous IOM committee. It reflects the deliberations of a new committee (Committee on Curriculum Development in Environmental Medicine) formed to recommend a curriculum in environmental medicine for undergraduate medical students. During the study, the committee considered both the content of an environmental medicine curriculum and the more difficult problem of implementing such a curriculum in medical education programs.

Although its charge was to focus on undergraduate medical education, it was difficult for the committee to conceive of accomplishing its objectives solely within those confines. The continuum of undergraduate, graduate, and continuing medical education seemed a more appropriate, if not necessary focus, because environmental medicine permeates the entire spectrum of medical practice and should similarly reach throughout the continuum of medical training. Some of the discussion in this report therefore refers to residency training and continuing medical education.

This report incorporates portions of the committee's interim report issued in 1993, and uses the six competency-based learning objectives set forth in that report as a central theme for recommending implementation strategies. The primary strategy, simply stated, is to integrate environmental medicine into existing courses and clerkships rather than defining and carving out new blocks or courses in an already crowded curriculum. The committee believes that the addition of new blocks or courses is not a viable option at this time, and that integrating environmental medicine is not only the most expeditious approach to achieving the stated objectives but is also the most appropriate approach given the pervasive and fundamental nature of the effects of the environment on health. The committee's own vision for training leaders in environmental medicine has thus been tempered with a strategy for implementing a realistic curriculum that all medical schools can embrace and deliver to their students.

Of great importance to the report's practical value as an immediate tool are Appendixes A, B, C, and D, which follow the main text. These provide detailed information on available educational resources and teaching aids and include 55 case studies that can be used to facilitate the integration of environmental medicine into both education and practice. The report articulates a coherent general program of action and provides practical advice to individual educators, students, and practitioners who either are interested in integrating more environmental medicine content into medical education or need resource information to help them address clinical situations.

In summary, the committee intends for this report to serve as a tool that can be used immediately by interested faculty, students, and practitioners who want to integrate and enhance environmental medicine in medical education and practice. In addition, we hope to convince others of the fundamental importance of environmental medicine, the need for integrating it into medical curricula, and the ease with which a curriculum can be enhanced with this information. The committee is confident that integrating environmental medicine into medical education will substantially enhance the competence of tomorrow's physicians in addressing the growing environmental health concerns of their patients and communities.

David P. Rall, M.D., Ph.D.
Chairman

Contents

EXECUTIVE SUMMARY 1

1 INTRODUCTION 5
  Definition and Scope of Environmental Medicine, 8
  Role of the Physician, 9
    Recent History, 9
    A Continuum of Roles, 10
  Origin and Organization of the Report, 11

2 CURRICULUM CONTENT 14
  Components of a Curriculum, 14
  Competency-Based Learning Objectives, 17
  Conclusions and Recommendations, 21

3 IMPLEMENTATION STRATEGIES 22
  Curriculum Access Points and Teaching Strategies, 24
    Competencies 1 and 2, 24
    Competency 3, 26
    Competency 4, 29
    Competency 5, 30
    Competency 6, 32
  Enhancing Faculty Awareness, 34
    Some Long-Term Strategies, 34
    Some Short-Term Strategies, 35

Conclusions and Recommendations, 38
    Integrating the Curriculum, 38
    Developing Faculty, 39
    Continuing Education, 40
    Evaluating Progress, 41

4 CHANGING MEDICAL EDUCATION 44
Calls for Reform in Medical Education, 44
Barriers and Opportunities, 45
    Barriers, 46
    Opportunities, 48
Conclusions and Recommendations, 51

5 CONCLUDING REMARKS 52

REFERENCES 54

APPENDIXES 59
A Taking an Exposure History, 61
B Medical School Courses and Clerkships: Access Points for Integrating Environmental Medicine, 97
C Case Studies in Environmental Medicine, 121
D Resources: Agencies, Organizations, Services, References, and Tables of Environmental Health Hazards, 909
E Committee and Staff Biographies, 971

ENVIRONMENTAL MEDICINE

Executive Summary

A pregnant woman voices a concern to her obstetrician during a routine prenatal visit. It seems that several women in her neighborhood have recently had babies with a variety of birth defects. She worries that the recently discovered well-water contamination in her community may be responsible, and she wants to know what she should do.

* * *

A 24-year-old salesman consults his physician with a two-month history of fatigue, joint pain, and occasional gastrointestinal symptoms. Approximately three months ago, he bought an 80-year-old house and started renovating the interior.

* * *

The public is increasingly concerned about potential environmental health hazards and often wants answers to very concrete questions, such as: Is the water safe to drink? Could my miscarriage be due to my work environment? What is the likelihood of having a child with birth defects due to exposure during pregnancy to my computer's electromagnetic field? (see Box 1.) Are the pesticides used on fruit harmful? Is living close to power lines harmful? Patients ask their physicians these questions because, in general, they trust them and value their advice. Unfortunately, physicians often lack adequate, appropriate information and training with respect to environmental risks and health.

The integral relationship between the environment and health necessitates the active participation of knowledgeable physicians in both clinical and community contexts. In 1988, the Institute of Medicine (IOM) examined the role of primary care physicians in occupational and environmental medicine and called for enhanced physician training and education in this area. Noting that primary care physicians are often the health professionals of first contact for patients with environmentally related illnesses, the IOM suggested that, "as a minimum, all primary care physicians should be able to *identify possible occupationally or environmentally induced conditions* and *make the appropriate referrals for follow-up*" (Institute of Medicine, 1988:63).

Today's challenge is to help medical students develop the knowledge and skills they will need to deal effectively with environmental health issues in clinical care and public health contexts. Doing this within the confines of an already stressed and overcrowded

Box 1. Reproductive Hazards and VDT Exposure

A 31-year-old woman, gravida 1, para 0, presents to her obstetrician at six weeks' gestation with concerns about her home computer. She is a graduate student at the local university and is working on her thesis. This work requires that she use the computer for up to six hours per day. She has heard that there may be an association between electromagnetic fields from video display tubes (VDTs) and adverse pregnancy outcomes. She does not want to take any risks, but she hopes to finish her thesis before the child is born. She asks her physician's opinion of the literature on VDT exposure and birth defects.

There have been many reported clusters of women working with VDTs in office settings who gave birth to children with birth defects. Reported defects were widely heterogeneous, including clubfoot, congenital heart defects, neural tube defects, and cleft palate. In addition, clusters of prematurity and spontaneous abortion have been reported. VDTs emit nonionizing radiation: light, radiowaves, and microwave radiation. While there is some concern about the association of nonionizing radiation in the form of electromagnetic fields and the risk of hematologic tumors, brain tumors, and adverse reproductive outcomes, the evidence is still very mixed. The evidence of an association between electromagnetic fields and specific cancers (e.g., leukemia, brain tumors) is much stronger at this time than the evidence of an association between these fields and reproductive risk. Most physicians do not feel that VDTs pose a significant risk of adverse pregnancy outcomes.

Patients' concerns about potential occupational or environmental exposures during pregnancy must always be taken seriously. If the clinician does not know the medical literature on the exposure in question, it is imperative that he or she research the issue before simply reassuring the patient. Maternal exposures to many things clearly increase the risk of adverse pregnancy outcomes. Lead, solvents, ethylene oxide, glycol ethers, carbon monoxide, radiation, prolonged standing, and drugs such as thalidomide and alcohol are all clear examples of reproductive hazards. Caution and awareness of the possibility of new reproductive hazards is important to prevent unnecessary reproductive tragedies.

Adapted from Bentur and Koren (1991), Paul and Himmelstein (1988).
See also case study number 53 in Appendix C for more information on reproductive and developmental hazards.

four-year undergraduate medical curriculum that has been described by some as unresponsive to societal changes and needs (Abrahamson, 1978; Marston and Jones, 1992; Pew Health Professions Commission, 1991) and reinforcing and expanding this knowledge and these skills during postgraduate residency training is a formidable challenge.

Although efforts at curriculum reform have failed in the past, medical education may be embarking upon a new era. There are renewed calls for change; those calls and the current evolutionary changes that are occurring in the health care system could be important driving forces for curricular change. Such change could include the integration and enhancement of environmental health in the curriculum.

To help prepare physicians for the emerging awareness of environmental health issues and their roles in addressing them, principles and concepts of environmental health must be taught and continually reinforced throughout undergraduate and postgraduate medical education and training. The committee believes, however, that specifying what should be taught is not as useful as describing what students should know and be able to do at the end of their training. With such competency-based objectives in mind, the committee recommends that all graduating medical students have the knowledge and skills listed below.

1. **Graduating medical students should understand the influence of the environment and environmental agents on human health based on knowledge of relevant epidemiologic, toxicologic, and exposure factors.**
2. **Graduating medical students should be able to recognize the signs, symptoms, diseases, and sources of exposure relating to common environmental agents and conditions.**
3. **Graduating medical students should be able to elicit an appropriately detailed environmental exposure history, including a work history, from all patients.**
4. **Graduating medical students should be able to identify and access the informational, clinical, and other resources available to help address patient and community environmental health problems and concerns.**
5. **Graduating medical students should be able to discuss environmental risks with their patients and provide understandable information about risk-reduction strategies in ways that exhibit sensitivity to patients' health beliefs and concerns.**
6. **Graduating medical students should be able to understand the ethical and legal responsibilities of seeing patients with environmental and occupational health problems or concerns.**

Consensus on the goals and content of a curriculum, such as the six competency-based learning objectives above, is a necessary but insufficient prerequisite for training medical students and residents in environmental medicine. Reasoned arguments for such a curriculum cannot alone ensure that it will be implemented. Other factors that affect the extent, quality, and success of implementation efforts include the availability of faculty time in an already overcrowded curriculum; support for teaching and curricular innovation; competing faculty and community concerns or interests; and budgetary constraints. Any strategy for implementing changes in the curriculum must be sensitive to these factors and include action at many levels.

At the medical school level, there is a need for knowledgeable and enthusiastic teachers, exciting teaching materials and methods, and creative and judicious use of curricular time. This will require that administrators who recognize the importance of the curriculum support ongoing faculty development and provide adequate rewards for the teaching faculty. All this may necessitate activities at many other levels, for example, expanded initiatives by federal agencies, residency review committees, and professional organizations. Practice barriers, such as lack of reimbursement for preventive services, will also require attention.

With these many counterpressures and demanding complexities in mind, we present a practical and simple approach to integrating environmental medicine into the medical curriculum. Rather than defining and carving out new blocks or courses in an already crowded curriculum, the committee favors an integrative approach to enhancing the environmental and occupational health content in undergraduate medical education. This is not only the most expeditious approach to achieving the competency-based objectives, but it seems to be the most appropriate as well given the pervasive and fundamental nature of environmental effects on health. Integration also highlights the relevance of environmental and occupational medicine to basic science and clinical studies and provides a vehicle for enhancing faculty awareness of those issues. As described in this report, instructors should be able to integrate environmental medicine into existing medical school courses and clerkships fairly easily.

To ensure the progressive enhancement of competency in environmental medicine in medical education and practice, the committee makes recommendations for the continued funding and expansion of programs that currently support research and training, such as Academic Awards and Center Grants. This enhancement should build on the success of current programs and include adequate funding to support reasonable progress in curriculum development, faculty development, and continuing education. In addition to the current activities, the committee recommends that consideration be given to establishing (1) a database of curricular materials for faculty and students, and (2) a speakers bureau in environmental medicine. Information about these activities and resources should be disseminated with vigor to help ensure the integration of environmental medicine into medical education and practice.

To facilitate integration and enhancement of environmental medicine in medical education, the report includes four appendixes that provide 55 case studies and other detailed information on available educational resources and teaching aids. Of particular utility will be the indexes in Appendix C, which guide the reader to cases in environmental medicine based on: (1) chemical agents and conditions, (2) medical school courses and clerkships/clinical rotations, (3) sentinel pathophysiological conditions, and (4) clinical signs, symptoms, and presenting complaints. The appendixes and case studies can and should be used to facilitate the integration of environmental medicine into both education and practice.

1

Introduction

At a local family practice clinic, several teenagers have presented with mysterious flu-like symptoms. One patient has been hospitalized and is in serious condition. The state health department is investigating the possibility of an illness related to rodent droppings and is interviewing the patients, their families, and their physicians.

* * *

For the third time in a month, a mother has brought her coughing, wheezing two-year-old daughter to the local emergency room. And, for the third time, the child is treated with bronchodilators and sent home with a diagnosis of asthma.

* * *

A reporter from the local newspaper is investigating a cancer cluster in the community. She is interviewing local physicians about the health effects of hazardous waste incineration and about electromagnetic fields.

* * *

The above examples are typical of the complex questions and situations associated with environmental factors increasingly encountered by physicians, who, in the course of their clinical training, may have had little preparation for dealing with them. Unaware of this potential shortcoming and faced with growing concerns about the potential health effects of environmental damage and contamination, people seek help from their physicians because, in general, they trust them and value their advice (McCallum and Covello, 1989). In order to respond appropriately, physicians need to be clinically competent in environmental medicine and dissuaded from the all too common practice of reflexively offering blanket reassurance to patients who feel they have been exposed to, or harmed by, an environmental toxicant.

The environment, including the work environment, is a critical factor for both health and disease. There is clear evidence that the health effects of environmental agents and environmental degradation are serious, whether they are direct, such as the effects of lead exposure on infant and child development (Bellinger et al., 1986), or indirect, such as the effects of climatic changes on vector distribution and ecosystem damage resulting in outbreaks of infectious disease (Epstein and Sharp, 1993; Leaf, 1989; see Box 2).

Box 2. Hantavirus Pulmonary Syndrome

A 19-year-old man presented to an emergency room in New Mexico in May of 1993 with an acute respiratory illness. The man was a marathon runner, previously in excellent health; his fiancée had died two days earlier with a severe respiratory illness. On exam, the patient was febrile, tachycardic, and tachypneic, but the rest of the physical exam was normal. The chest x-ray was clear, and laboratory findings were unremarkable. The patient was sent home on erythromycin and amantadine. Over the next two days the symptoms continued, and the patient developed vomiting and diarrhea. Repeat physical exams showed little change and clear lung fields. The next day the patient developed rapidly progressive shortness of breath and a cough productive of copious yellow sputum. Over several hours the patient developed fulminant respiratory failure and died.

This was the second person struck by the now famous Hantavirus pulmonary syndrome outbreak in the southwestern United States in the summer of 1993. The outbreak of the disease can be traced to unusual environmental conditions in the area. A rainy summer the previous year led to a large increase in the crop of piñon nuts; this in turn led to a rodent population explosion in the area. We now know that various species of rodents throughout the United States carry this strain of Hantavirus, and unrecognized cases among people may have occurred previously. The environmental factors that led to the increase in the reservoir population, and to inevitably closer contact between people and the rodents, resulted in the "emergence" of the disease at that time and place.

What may seem like subtle environmental changes can clearly have a significant impact on disease spread. The penetration of humans deep into tropical rainforests may bring people into contact with previously unknown diseases (HIV may have emerged in this way). Jet travel allows infected humans to spread disease rapidly around the world. Global warming may greatly expand the range of many vector populations, such as the Asian tiger mosquito, which was recently introduced into the United States in a shipment of wet automobile tires, and is now rapidly spreading throughout the southern United States. Finally, the enormous population density in many third-world cities provides a setting ripe for the rapid transmission of many diseases. All of these environmental factors are cause for concern about future outbreaks or epidemics of infectious disease.

Adapted from Duchin et al. (1994).
See also case study 17 in Appendix C.

Although the precise impact of environmental illness and injury is virtually impossible to compute—partly because adequate surveillance mechanisms do not exist and partly because environmentally related disease often goes unrecognized as such—there is enough undisputed evidence of the relationship between environmental exposure and disease to justify moving from concern to action. For example, the Centers for Disease Control and Prevention estimates that 3 million preschool children in the United States have blood lead levels greater than 10 μg/dl, a level associated with neurotoxic effects (Centers for Disease Control, 1991). The prevalence of asthma, especially among children (Larsen, 1992; National Center for Health Statistics, 1989), and of waterborne diseases from chemical contamination is increasing (U.S. Department of Health and Human Services, 1991). There is growing concern that a substantial fraction of cases of cancer and a variety of adverse reproductive outcomes may be associated with environmental agents (Landrigan, 1993; Paul, 1993). Similarly, there is also growing concern about the possible relationship between pesticides and breast cancer (Wolff et al., 1993). In addition, illness and injury related to occupational exposures and conditions continue to take their toll on the U.S. workforce, with 6.3 million job-related illnesses and injuries reported by the private sector in 1991 alone (U.S. Department of Labor, 1993).

Despite the association between environmental contaminants and adverse health effects, the use, release, and disposal of potentially toxic chemicals into the environment continues. In 1991, U.S. industry reported the release of 3.39 billion pounds of potentially toxic chemicals into the air, water, and soil (U.S. Environmental Protection Agency [EPA], 1993). Also in 1991, more than 31,000 sites had been reported to the EPA as potentially in need of cleanup; 1,189 of these were designated as hazardous waste (Superfund) sites.

In addition to these specific examples of the important relationship between the environment and health, there are other reasons why primary care physicians need to understand the basic concepts of environmental medicine. First, the increased use of right-to-know laws in the context of the workplace, the community, and in the labeling of consumer products means that the public will have more information about chemical threats. The increased availability of information will make it more likely that patients will appear in their physicians' offices seeking advice about the possible relationship of these chemicals to their current symptoms or their potential for future adverse effects.

Second, recent advances in molecular biology suggest that medical science will soon be able to tease out the role of genetic factors in common diseases. If genetic factors cannot be identified or are found to provide a less than full or satisfactory explanation about why individuals contract a particular disease, the need to focus on environmental factors will grow. These same advances in biology pose every likelihood of providing direct insights into the relationship between environmental factors and common diseases.

Finally, physicians' skills and knowledge must be adequate not only for treating their patients but also for explaining their actions in public health, legal, and regulatory arenas, if necessary. The magnitude of the production, use, release, and disposal of known and suspected toxic agents gives some urgency to the need for physician participation in these contexts.

Thus, given the widespread distribution of environmental hazards and their potential effect on the health of individuals and populations, one can expect only increasing demand for information, services, and treatments from medical professionals in the future. By taking an active role in educating and preparing their students in environmental medicine today, medical schools can demonstrate leadership in caring for people adversely affected by or concerned about environmental agents.

DEFINITION AND SCOPE OF ENVIRONMENTAL MEDICINE

The potential adverse health effects of environmental factors are generally well recognized by the medical community but not always well understood. In its broadest sense, the environment is at least partially responsible for all diseases except those determined solely by genetics, and includes such factors as housing, nutrition, socioeconomic status, and life-style. For the purposes of this report, however, the Committee on Curriculum Development in Environmental Medicine defines "environment" and "environmental medicine" more narrowly and in concert with the definitions in the 1988 Institute of Medicine (IOM) report *Role of the Primary Care Physician in Occupational and Environmental Medicine*. That is, the committee's use of the term environmental medicine refers to diagnosing and caring for people exposed to chemical and physical hazards in their homes, communities, and workplaces through such media as contaminated soil, water, and air. This definition excludes diseases caused by tobacco use, alcohol, diet, or other life-style factors as well as conditions that are a direct consequence of genetics, violence, and iatrogenically caused illness or injury. As stated in the 1988 report, this definition is not meant to diminish the importance of these factors in disease, but to reflect a concern and strong belief that non-life-style environmental factors are equally deserving of study and attention; in this view, when taking a history or formulating a diagnosis, physicians should consider non-life-style environmental factors, such as workplace, home, and community exposures, as well as the "traditional" environmental factors such as alcohol and nicotine.

Occupational exposures are some of the most important environmental exposures, and many of the concepts and principles of occupational medicine are directly relevant and applicable to environmental medicine. Like occupational medicine, which is limited to the workplace environment, environmental medicine is prevention oriented. In essentially all cases, environmentally induced illness and injury are preventable, largely through nonmedical risk management interventions, such as engineering design, product substitution, and education. Thus, many of the most effective prevention activities of environmental medicine occur outside the traditional clinical paradigm. However, many of the interventions flow directly from an individual physician–patient encounter that identifies a health problem or risk attributable to specific environmental factors or conditions. The clinical encounter provides a unique opportunity for the clinician to practice prevention-oriented primary care. Moreover, a single diagnosed case of environmental or occupational illness often serves as a sentinel, alerting the public health community that prevention has failed, that other members of the population may be at risk, and that intervention is needed (Rutstein et al., 1983).

ROLE OF THE PHYSICIAN

Recent History

For many years, physicians and other health care providers have been largely uninvolved in environmental issues related to human health. Certainly, their undergraduate and graduate medical education did little to encourage or prepare them for such involvement. Indeed, the paucity of their training in this area has been well documented (Institute of Medicine, 1988; Levy, 1985). Surveys have shown, for example, that in 1985 only 50 percent of U.S. medical schools included occupational and environmental health in their curricula, with an average of only four hours being taught over four years (Levy, 1985). By 1992, improvement was only modest, with 66 percent of schools requiring about six hours of study in occupational and environmental health (Burstein and Levy, 1994). A survey of 89 departments of internal medicine at U.S. medical schools found that only 22 percent offered occupational medicine experiences, almost all of which were elective (Cullen and Rosenstock, 1988). Resident training in the broader area of environmental medicine has been even less common.

Moreover, a review of the curriculum catalog from the Association of American Medical Colleges (1993) indicates that courses in environmental medicine are rare and, when offered, are usually elective in nature, competing with many popular alternatives.

Medical education's focus on the individual patient with disease has not encouraged faculty and students to step beyond the medical model and consider the health of the population—be it the physician's practice population, a worker population, a neighborhood or community population, or the population of a state, region, or nation. Blame might also be placed on the many well-known deficiencies of the medical education system—a system that has compartmentalized teaching and learning into rigid disciplines, focused on information transfer instead of information management and problem solving, and rewarded research over teaching (Association of American Medical Colleges, 1983; 1992a).

There are other explanations for physician noninvolvement, however. Practical constraints are enormous; physicians often just do not have the time to get involved in their patients' environmental or occupational health problems, many of which are complex and time consuming. The technical aspects of such environmental problems as air pollution, occupational disease, and toxic emissions can be daunting. Moreover, reimbursement for time spent on environmental questions is often lacking, and administrative burdens such as those imposed by worker's compensation cases may be formidable (Institute of Medicine, 1988). Indeed, the realities of clinical practice reinforce the practitioner's need to focus on the individual patient with disease. Furthermore, in the area of environmental (and occupational) health, the possibility of interaction with the legal system looms large in the minds of some physicians; however remote, this possibility can discourage some physicians from pursuing an environmentally related diagnosis.

There may also be philosophical, political, social, and cultural explanations for lack of physician involvement. For example, it has been suggested that physicians are sometimes uncomfortable with the priorities of environmental activists (Guidotti, 1991). With growing public awareness and concern about the health effects associated with environmental agents, however, physicians and other health care providers can no longer avoid involvement in environmental medicine.

A Continuum of Roles

In 1988, the IOM examined the role of primary care physicians in occupational and environmental medicine and, as a result, called for enhanced physician training and education in this area. Noting that primary care physicians are often the health professionals of first contact for patients with environmentally related illnesses, the IOM suggested that as a minimum, all primary care physicians should be able to identify such illnesses and refer patients appropriately for follow-up (Institute of Medicine, 1988). Two subsequent IOM reports on occupational and environmental medicine addressed physicians' needs for medical information (Institute of Medicine, 1990) and the physician shortage in occupational and environmental medicine (Institute of Medicine, 1991).

Following up on the IOM's 1988–1991 series of reports, this committee has described a continuum of roles that physicians can assume in the area of environmental medicine (see Box 3).

At one end of the continuum is the role of the environmentally competent clinician. At the very minimum, this role includes the ability to identify possible environmentally related conditions to make the appropriate referrals for evaluation and follow-up care. To conduct even this limited activity, physicians will need to obtain certain knowledge and develop certain skills that are not routinely provided in U.S. medical education. With this and additional training, clinical competence can be expanded to include the ability to appropriately diagnose, treat, and manage patients with environmentally related disease as well as the ability to conduct basic and clinical research and to educate and counsel patients about environmental risks. The latter function will become increasingly important as patients seek advice from their physicians about the safety of drinking water, pesticide-contaminated food, "sick" buildings, "toxic" carpets, hazardous working conditions, and suspected clusters of cancer, miscarriage, and other diseases.

Moving beyond this clinician-educator role toward the other end of the continuum, physicians can expand into areas of increasing activism in relation to individual and pub-

Box 3. A Continuum of Roles

A continuum of roles illustrates several levels and types of activity for physicians in the area of environmental medicine. Physicians can:

- provide clinical care and advice for individual patients in an office setting (the environmentally competent clinician);
- be advocates for individual patients by communicating with employers, landlords, local public health authorities, and other relevant agencies, as needed;
- become involved at the community level by advising and educating local citizens, groups, colleagues, public health officials, and community leaders about environmental health; and
- participate in public health policymaking at the local, national, or international level.

lic health and the environment. Indeed, there have been calls for "environmentally literate" physicians who will serve as spokespersons and leaders in environmental issues (Cortese and Armoudlian, 1991; Guidotti, 1991; Leaning, 1990; McCally and Cassel, 1990).

The extent of an individual physician's activity in environmental medicine is, in large measure, a matter of personal preference. However, there is little doubt that basic clinical competence in environmental medicine is essential for all physicians. As individual and community concerns about the environment grow, physicians will encounter inquisitive, confused, at-risk, and diseased patients in their offices—patients with questions, concerns, complaints, signs, and symptoms. Medical schools need to respond to society's growing environmental concerns by developing educational programs that teach clinicians how to meet these needs. An important long-term goal in this regard would be the establishment of a network of specialists in the field to whom referrals can be made. The Association of Occupational and Environmental Clinics (see Appendix D) provides a good example of a national network of clinical facilities dedicated to research and education as well as to the prevention and treatment of occupational and environmental diseases.

ORIGIN AND ORGANIZATION OF THE REPORT

In 1992, at the request of the Agency for Toxic Substances and Disease Registry (ATSDR) of the U.S. Public Health Service, and with subsequent support from the Environmental Protection Agency (EPA) and the National Institute for Occupational Safety and Health (NIOSH), IOM convened the present committee to continue and build upon previous work by the IOM in defining and fostering environmental medicine. The committee was given six specific tasks:

- define the scope of activities in environmental medicine,
- identify essential competencies in environmental medicine,
- develop learning objectives in environmental medicine,
- recommend methods for faculty development,
- identify resources for faculty training in environmental medicine, and
- recommend methods for integrating environmental medicine into medical education and evaluating its effectiveness.

The committee convened a public workshop in May 1993 to help begin the process, and issued an interim report in the fall of 1993 that recommended establishing six competency-based learning objectives, on which the present report builds.

Although the committee's charge was to focus on undergraduate medical education, it was difficult for the committee to conceive of accomplishing its objectives solely within those confines. The context of the continuum of undergraduate and graduate medical education seemed more appropriate because environmental medicine permeates the entire spectrum of medical practice and should similarly reach throughout the continuum of medical training. Some of the discussion in this report therefore refers to residency training and continuing medical education.

The chapters and appendixes that follow reflect the committee's further pursuit of its six tasks. The report articulates a general program of implementation strategies and provides immediate practical advice to individual educators, students, and practitioners who either are interested in integrating more environmental medicine content into medical education or need resource information to help them address clinical situations.

Chapter 2 begins by laying the foundation for an environmental medicine curriculum centered on six competency-based learning objectives. Chapter 3 then uses these objectives as a framework for identifying likely access points in the curriculum for integrating environmental medicine into today's medical studies. Chapter 4 addresses both the barriers to implementing such a curriculum and the opportunities for reducing these barriers. Chapter 5 presents concluding remarks that summarize some of the events that led to this report and the committee's optimism with respect to the ease with which medical education can incorporate an enhancement of the training of environmental medicine. Recommendations for integrating an enhanced program of environmental medicine throughout our system of medical education and practice appear at the ends of the individual chapters (i.e., Chapters 2–4).

To enhance the report's practical value, four appendixes are included that provide detailed information on available educational resources and teaching aids. They can be used to facilitate the integration of environmental medicine into both education and practice. Appendix A contains a case study developed by the ATSDR on "Taking an Exposure History"; it is a good example of a tool for teaching or learning how to elicit a good environmental history. Appendix B, "Medical School Courses and Clerkships: Access Points for Integrating Environmental Medicine," illustrates the relevance of and opportunities for integrating environmental medicine into common medical school courses and clerkships/clinical rotations. It also identifies case studies from Appendix C that could be used in these courses or contexts. Appendix C, "Case Studies in Environmental Medicine," contains 55 case studies that should be useful in teaching and learning. This appendix has four indexes to help the reader determine the most relevant cases for a particular course, clerkship, or other purpose. The case studies are indexed by (1) chemical agents and conditions; (2) common medical school courses and clerkships/clinical rotations; (3) sentinel pathophysiological conditions; and (4) clinical signs, symptoms, and presenting complaints. Appendix D, "Resources: Agencies, Organizations, Services, References, and Tables of Environmental Health Hazards," identifies various sources of information, including governmental agencies (federal and state), environmental associations and organizations, regional and international information services, computerized information services, resources by selected topic (e.g., air pollution, clean water, and radon), general reference books and journals, a medical school listing of environmental medicine activities, and several tables of toxic chemicals, health effects, and occupational exposures. It is our hope that these materials and resources will facilitate the integration and enhancement of environmental medicine in medical education.

2

Curriculum Content

In contemporary society, the development of a basic understanding of the environment and health begins early in childhood, and tomorrow's students will likely enter medical school more sensitive to environmental concerns and, perhaps, with a basic fund of knowledge about the environment and its relation to human health. Our challenge is to ensure that our current and future medical students develop the knowledge, skills, and attitudes needed to deal effectively with environmental health issues in clinical care and in the public health context. Doing this within an undergraduate medical curriculum that has been described as rigid, ossified, stagnant, and unresponsive to societal changes and needs (Abrahamson, 1978; Marston and Jones, 1992; Pew Health Professions Commission, 1991) and reinforcing and expanding this knowledge and skill in the residency years is a formidable challenge.

COMPONENTS OF A CURRICULUM

Although efforts at curriculum reform have failed in the past, medical education may be embarking upon a new era. There are renewed calls for change; those calls and the current evolutionary changes that are occurring in the health care system could be important driving forces for curricular change. Such change could include the introduction and integration of environmental health into the curriculum.

Defining the content of a curriculum in environmental medicine is far easier than ensuring its implementation and integration into existing medical education programs. The latter requires effective leadership and faculty resources, commitment, and skills in addition to an educational climate and format open to experimentation, adaptation, and change.

Developing a curriculum in environmental medicine also requires thoughtful specification—in concrete and, preferably, behavioral terms—of what graduating medical students should know, be able to do, and be sensitive to in the area of environmental health. These "competencies" should also reflect related societal and patient needs. In emphasizing competencies, the committee is expressing its belief that specifying what should be taught is not as useful as describing what students should know and be able to do at the completion of training.

Past recommendations for creating or enhancing a medical school curriculum in environmental health often focused on occupational health. Although many of the underlying principles and concepts of environmental and occupational health are the same, there are also significant differences, some of which may require additional or different learning objectives. Such differences include the absolute level of risk, sources and routes of exposure, possibilities for intervention and environmental manipulation, and a number of administrative, legal, and political issues (Cullen and Figueroa, 1990). Another major difference between environmental and occupational health is the broader range of populations at risk in the former. The expanded focus of environmental health provides the opportunity to involve more clinical specialties in the teaching of environmental health, such as pediatrics, obstetrics/gynecology, and geriatrics.

Current discussions about a curriculum in environmental medicine reveal considerable agreement about certain fundamental components. In its 1988 report, IOM suggested (pp. 47–48) that didactic and clinical training in occupational and environmental medicine provide:

- solid grounding in epidemiology and toxicology;
- an understanding of the concept of risk and its application to groups and individuals;
- a method of obtaining an occupational and environmental health screening history;
- concepts of dose response and other factors that contribute to exposure and host response;
- knowledge and skill in finding and using information about environmental and occupational diseases; and
- sensitivity to special medical, ethical, legal, and economic factors in caring for patients with environmental and occupational diseases.

Other groups have echoed these suggestions and have added several others, such as a focus on risk assessment and risk communication in medical education (American College of Physicians, 1990) and new methods for improving students' skills in taking occupational and environmental histories (Kipen and Craner, 1992).

But in addition to the points of overlap and agreement among interested groups, there are other concerns and proposals that require examination. For example, because solutions to individual and community environmental health problems are often preventive and political in nature, students need to learn about the broader array of interventions available in environmental health; an overreliance on the medical model and its clinical interventions may be ineffective or applied too late in the disease process. In simple concrete terms, early lead abatement in the home is preferable to chelation later. Students need to learn how to tap resources in the community to assist with intervention. These resources include public health departments and other government agencies, voluntary organizations, community and consumer groups, and an array of environmental health professionals (see Appendix D).

Similarly, discussions of the concept of risk should go well beyond its epidemiologic definition and its application in risk assessment. Students also need a basic understanding of the elements of risk perception, and they must begin to develop an ability to effectively communicate the concept of risk to patients, especially in the clinical setting.

Another important aspect of the discussion that merits attention concerns the fact that environmental medicine is a field in which information is often missing (e.g., about exposure, dose, risk, and health effects) and in which the economic and political stakes of public action or inaction are often high. Thus, the ability to make decisions in the face of considerable uncertainty is very important. Physicians must be prepared to counsel their patients and communities about environmental health hazards even though little may be known about their long-term health effects. They also need to appreciate how values (their own and those of others) can influence the questions asked, the problems studied, the recommendations made, and the actions taken.

A review of both the points of clear agreement about the components of a curriculum for environmental medicine and the more complex questions of its behavioral, social, and political aspects suggests the following conclusion: any level of physician involvement in environmental medicine, no matter how simple, must rest upon a basic level of competence, which, if realistically defined, should be addressed by all undergraduate and graduate medical education programs. Helping students achieve this basic level of competence should be the primary goal of the curriculum. A realistic curriculum in environmental medicine will (1) identify a small set of competencies, (2) fit comfortably within existing curricular structures, (3) be reinforceable by attending faculty and residents during clinical rotations, and (4) focus on the area that is unique to the physician's role in environmental health—that is, preserving human health. However, the fundamental breadth and potential ramifications of environmental health issues beyond the realm of clinical medicine require enough flexibility in the curriculum to accommodate students who may wish to take broader, more active roles in environmental medicine and research. To prepare physicians to achieve these goals and fill these roles, this committee has defined six competency-based objectives that are considered reasonable, achievable, reinforceable, and relevant to the physician's role in environmental medicine. These objectives, slightly modified from the committee's interim report (Institute of Medicine, 1993a), provide the framework for developing an implementation strategy described in Chapter 3.

COMPETENCY-BASED LEARNING OBJECTIVES

The integral relationship between the environment and health creates a need for physicians to participate actively in both clinical and community environmental health issues. As expressed earlier, there are things graduating medical students should know, be able to do, and be sensitive to in the area of environmental health. To help physicians acquire and heighten these "competencies," principles and concepts of environmental medicine must be taught and continually reinforced throughout medical education.

The committee is concerned about the current handling of public health and epidemiology courses in the medical curriculum, both in terms of when they are taught and the lack of emphasis placed on them. These topics are generally taught during the first two years of medical school, along with a plethora of basic science courses that often seem devoid of clinical relevance. Moreover, basic science, epidemiology, and public health are seldom explicitly revisited in the clinical years and in the three-plus years of residency training that follow.

It has already been observed that evolutionary changes in the health care system and pressures to reform medical education may create new opportunities to enhance the teaching of environmental medicine in medical schools. Physicians with expertise and interest in occupational, environmental, and preventive medicine should take the lead in developing creative teaching strategies and in serving as environmentally conscious and active role models for students and residents.

Guided by its belief that specifying what should be taught is not as useful as describing what students should know and be able to do at the end of their undergraduate training, the committee recommends that all graduating medical students have the knowledge and skills described in the following six competency-based learning objectives:

Competency 1. **Graduating medical students should understand the influence of the environment and environmental agents on human health based on knowledge of relevant epidemiologic, toxicologic, and exposure factors.**

Rationale. There is a clear relationship between the environment and human health. Healthy environments, including workplaces, promote good health, and contaminated or unhealthy environments promote disease. Many types of environmental agents cause, or put people at risk for, acute and chronic health effects. Although physicians are often well educated in the clinical significance of infectious agents and vector-borne diseases, they often have limited understanding of diseases caused by chemical or physical agents in the environment. A working knowledge of toxicology, epidemiology, and exposure analysis should be an important element in the training of medical students and residents (see Box 4).

Box 4. Methemoglobinemia from Nitrate Exposure

A two-month-old infant was brought by her mother to a small clinic in a rural farming area. The child had a poor appetite for the past two weeks and had persistent loose stools. The mother noted an increasing bluish discoloration around the child's lips. Over the past few days the infant was crying and fretful, was vomiting and having frank diarrhea. On history, the child was bottle-fed, with formula diluted with tap water. The water source was a well. No other family members were ill.

On exam the child was afebrile, but notably tachypneic, tachycardiac, cyanotic, and drowsy. The child had a new grade II/VI systolic murmur, but the lungs were clear and the rest of the exam was fairly unremarkable. There was no improvement despite administration of 100% oxygen and fluids. The child began to have seizures, cardiac monitoring showed ventricular ectopia, and there was evidence of renal shutdown.

Nitrates avidly oxidize the ferrous iron (Fe^{++}) in deoxyhemoglobin to the ferric (Fe^{3+}) state. This transformation produces methemoglobin, which cannot reversibly bind or transport oxygen. Fetal hemoglobin is more susceptible to oxidation than adult hemoglobin. The resulting clinical picture is one of hypoxia, with CNS depression leading to coma, circulatory failure, and cyanosis.

Nitrates and nitrites are common contaminants of water supplies in farming areas due to runoff of fertilizers in ground water. Contamination of water supplies from animal wastes or from sewer systems also leads to these nitrogen products in water. Preserved meats, and certain medications, particularly topical silver nitrate, which is commonly used for burn therapy, can also lead to methemoglobinemia in infants.

Adapted from Agency for Toxic Substances and Disease Registry, 1991.
See also case study 26 in Appendix C.

Competency 2. **Graduating medical students should be able to recognize the signs, symptoms, diseases, and sources of exposure relating to common environmental agents and conditions.**

Rationale. Several environmental agents are common causes of disease and disability, and others are increasingly associated with acute and chronic health problems.

An understanding of a few common disease-exposure relationships will provide a broad foundation for an improved general understanding of how environmental agents can affect a variety of organ systems, cause different types of health effects, and be amenable to prevention and control. Examples of important common environmental agents and conditions include lead, organophosphate pesticides, solvents, carbon monoxide, ozone, methylmercury, noise, and asbestos. The choice of specific agents for attention in the curriculum will depend on the medical school, faculty experience and interest, and local environmental and occupational problems.

Competency 3. **Graduating medical students should be able to elicit an appropriately detailed environmental exposure history, including a work history, from all patients.**

Rationale. An adequate environmental exposure history is needed to assess individual risk for prevention purposes, to identify environmental contributors to symptoms for diagnostic and therapeutic purposes, and to develop a sensitivity to the environmental conditions in a community that may contribute to ill health. The environmental history (including work history) also provides a vehicle for enhancing the patient-physician relationship. It creates an opportunity for patients to bring their own expertise about their workplace, home, and community environments to the relationship.

Physicians routinely elicit past medical, family, and at least partial smoking histories, but they seldom inquire about the details of a patient's occupational and environmental exposures. Diseases caused by environmental and occupational exposures are frequently similar to diseases of different etiology, and the exposure history is usually the key to distinguishing between them. Specific skills and experience are needed to help accurately identify these etiologic agents. Treatment may be ineffective if the connection is not recognized and the exposure is not controlled; prevention and risk-reduction activities depend on proper hazard identification (see Box 5).

Competency 4. **Graduating medical students should be able to identify and access the informational, clinical, and other resources available to help address patient and community environmental health problems and concerns.**

Rationale. The environmental and occupational history may elicit information about exposures and conditions unfamiliar to the physician. At a minimum, physicians should know where to refer patients with a suspected environmental problem or concern. If they are willing to pursue the evaluation themselves, physicians must know where to turn for information and assistance. Such resources include written and database sources; colleagues; specialists in occupational and environmental medicine, and in public health; government agencies; employers and manufacturers; and unions and workers (see Appendix D).

Box 5. Asbestos Disease

A 53-year-old woman presented to the emergency room with acute onset of pleuritic chest pain and dyspnea. Chest x-ray revealed a spontaneous right sided pneumothorax, fibrotic changes in her left lung field, and pleural plaques. The patient complained of gradually increasing dyspnea on exertion over several years. Upon close questioning, she recalled that she had helped her husband build two bungalows thirty years ago and that she had held sheets of asbestos while he sawed them to size.

A 42-year-old social worker presented with right side chest pain and dyspnea. Chest x-ray revealed a right pleural effusion, and fibrotic changes throughout the lungs. PPD was positive, so she received a presumptive diagnosis of tuberculosis and was started on therapy. Her symptoms worsened, with rapidly increasing dyspnea. Thoracentesis was then performed and revealed 2,500 ml of bloody, exudative fluid. Thoracoscopic biopsy confirmed the diagnosis of mesothelioma. The patient lived, as a child, near an asbestos mine in Johannesburg, South Africa. Her father worked in the mine, and wore his dusty clothes home from work; he also died of mesothelioma.

Asbestos is an important example of a potent toxin leading to fibrosis and cancer in workers and those exposed through their environment. The pathophysiology of attack on the long fibers by the cellular immune system, and damage to the lungs from repeated degranulation of neutrophils which are unable to engulf the fibers, is a good example of how the interaction between the body's defenses and the foreign substances cause the disease. Asbestos is only harmful insofar as the immune system attacks, then re-attacks the fibers, thereby damaging adjacent lung tissue. Other environmental chemicals are metabolically activated into potent toxins. Thus, it is always important to consider the metabolic fate of the toxin, the immunological response, the excretion of the toxin, and to take a thorough environmental history.

Adapted from Elmes (1966), Wagner et al. (1960).
See also case study 3 in Appendix C.

Competency 5. **Graduating medical students should be able to discuss environmental risks with their patients and provide understandable information about risk-reduction strategies in ways that exhibit sensitivity to patients' health beliefs and concerns.**

Rationale. The public is increasingly concerned about environmental health hazards, and community-based survey data show that physicians are considered the most trusted (but least informed) sources of information about the risks of chemical exposure. The ability to counsel patients about environmental health risks will require a sound knowledge base, an appreciation of the complex nature of patients' concerns about environmental health hazards, and excellent communication/counseling skills.

Competency 6. **Graduating medical students should be able to understand the ethical and legal responsibilities of seeing patients with environmental and occupational health problems or concerns.**

Rationale. Many states have reporting requirements for occupational and environmental diseases. Beyond compliance with legal reporting requirements, physicians may have ethical obligations to report environmentally related conditions to local authorities, especially when other members of the public may be at risk. In addition, patients may need their physicians' assistance in obtaining the compensation and remediation allowed them by law. Physicians should have a basic understanding of their legal and ethical responsibilities and know where to go for help.

CONCLUSIONS AND RECOMMENDATIONS

With the common acknowledgment that the environment is a vitally important factor in health and in a wide range of illnesses, it follows that every medical school graduate should be knowledgeable and competent in the basic elements of environmental medicine. Thus the committee believes that every medical school graduate should master the six competencies in environmental medicine described in this report and integrate environmental and occupational history-taking into daily practice. Employing this knowledge and these competencies will provide a basis for a more appropriate interaction with patients and the community regarding the impact of environmental medicine and will expand physicians' knowledge and improve their clinical expertise.

The committee believes that developing the ability to obtain a thorough environmental and occupational history is a fundamentally important component of the competencies, because if done correctly, such a history provides the primary information needed for diagnosis, referral or treatment, and prevention of environmental and occupational illnesses and injuries. A focus on the history can, indeed should, lead to the knowledge, skills, and attitudes encompassed in the other competencies. The elements of such a history have been well described, and a variety of forms and tools have been developed for both teaching and practice purposes (Agency for Toxic Substances and Disease Registry, 1992; American Lung Association of San Diego, 1983; California Public Health Foundation, 1992; Connecticut Department of Health Services, 1992; Goldman and Peters, 1981). Appendix A of this report contains a good example of such a history that was prepared by the ATSDR and peer reviewed by several experts in the field.

Direct discussion of the foregoing competency-based objectives continues in Chapter 3, where each competency is discussed in terms of likely access points in the curriculum for their integration and possible teaching strategies. Chapter 4 then considers the general structure and characteristics of medical education today and reflects on both the barriers to and opportunities for introducing these six objectives into the curriculum.

3

Implementation Strategies

This chapter describes an integration approach to enhancing the environmental medicine content of the medical school curriculum. However, at the outset, it is important to emphasize the critical need for an interested and willing faculty with competence in environmental medicine. Without this competence and commitment, the most creative and relevant curriculum will have no more life than the paper it is printed on. With the paucity of environmental medicine expertise in medical schools (Institute of Medicine, 1988; 1993a), any implementation strategy must address the need to expand and enhance the cadre of medical school faculty with this expertise. Without at least one champion to advance the cause of environmental medicine in curriculum committees and departments, even modest efforts to create an environmental focus in existing courses and clerkships are unlikely to succeed. We address this fundamental necessity in greater detail later in this chapter.

To begin the task of enhancing the content of environmental medicine in the curriculum of any particular medical school, it is advisable and reasonable to first inventory and assess what is currently in place. Once it has been established that a content area, such as environmental medicine, is underemphasized, then a basis for action is created. Building a consensus on a current problem or deficiency, however, is often easier than gaining support for a specific solution. Proposals for specific solutions may provoke claims that such solutions have been tried and failed. While such claims may be true, individuals and communities continue to be concerned with environmental issues and have a growing understanding and appreciation of the influence of the environment on health and the need for action.

Developing an inventory also provides a critical opportunity to identify and assess faculty interest and expertise in environmental health. The importance of personal contacts in creating learning opportunities cannot be over-stated. Allies and interest may be found in unexpected places—from the biochemist by profession who wants to build more clinical relevance into his/her course to the busy family practitioner who is stymied by patients with symptoms related to indoor air quality.

Once an inventory establishes a need within a given institution, sources of support must be identified. Influential support, such as from a departmental chair, a prominent investigator, a favorite instructor, or a highly regarded clinician, can be very helpful. Members of the student body should not be overlooked; they are often powerful advocates for environmental issues and for understanding their effects on health. It is also important to know the location and basis of opposition, because such understanding can expedite discussions and facilitate resolutions.

In order for tomorrow's physicians to have the knowledge, skills, and attitudes needed to practice medicine in a society in which the environment is of increasing concern, environmental medicine must be integrated into medical school education. Toward this end, the committee recommends that all graduating medical students master the six competencies (described in Chapter 2 of this report) that encompass the requisite core knowledge and skills. Where and when these competencies will best be learned depends on the structure and format of each individual school's specific curriculum. (As has been said numerous times by committee member Brownie Anderson, "If you've seen one medical school, you've seen one medical school.") Regardless of the specific structure and format, however, the fundamental content of the medical curriculum is relatively consistent and amenable to the integration or enhancement of environmental medicine concepts and information.

Rather than defining and carving out new blocks or courses in an already crowded curriculum, the committee favors an integrative approach to enhancing the environmental and occupational health content in undergraduate medical education. This is not only the most expeditious way to achieve the competency objectives, but it also seems to be the most appropriate given the pervasive nature of the effects of the environment on health. Integration also highlights the relevance of environmental and occupational medicine to basic science and clinical studies, and provides a vehicle for enhancing faculty awareness of the issues. Moreover, instructors should be able to integrate environmental medicine into existing disciplines and medical school courses and clerkships fairly easily.

To show how the six competencies can be integrated into existing programs, this chapter discusses each one in terms of likely access points in the curriculum and possible teaching strategies. The competencies can be grouped into those that are more knowledge oriented (competencies 1-3) and those that focus more on skills (competencies 3-6; competency 3 overlaps both groups)—similar to the basic science/preclinical and clinical years found in a traditional medical curriculum. The chapter concludes with some institutional strategies and suggestions for enhancing faculty awareness of the growing need to develop educational opportunities for student achievement of these competencies.

The chapter is supplemented by Appendix B, which provides suggestions for integrating environmental medicine into specific courses and clerkships, and Appendix C, which contains numerous case examples. In order to facilitate the identification and use of these cases for different teaching purposes, they are indexed (in the front of Appendix C) according to chemical agent, specific courses and clerkships, sentinel pathophysiological conditions, and clinical signs, symptoms, and presenting complaints. The actual content or teaching method used for presenting this information and achieving the related learning objectives will and should vary according to faculty interest and expertise, institutional resources and constraints, and the ongoing level of curriculum change.

CURRICULUM ACCESS POINTS AND TEACHING STRATEGIES

We consider competencies 1 and 2 together here because they are primarily knowledge-based. The courses that would most appropriately begin to introduce the environmental and occupational material needed to achieve these competencies can usually be found in the basic science area of the medical curriculum; however, the application of this knowledge must be continually reinforced during the clinical years.

Competencies 1 and 2

Competency 1. **Graduating medical students should understand the influence of the environment and environmental agents on human health based on knowledge of relevant epidemiologic, toxicologic, and exposure factors.**

Competency 2. **Graduating medical students should be able to recognize the signs, symptoms, diseases, and sources of exposure relating to common environmental agents and conditions.**

Basic Science Courses

In most medical schools, the first two years are organized into either basic science or multidisciplinary courses that are organ-based in their focus. In either context, it is relatively easy to teach environmental medicine content without requiring additional time in the curriculum and without much more effort. For example, a basic science faculty member teaching about oxygen transport could illustrate the principles of oxygen-hemoglobin binding by comparing the mechanisms of the binding capacity of oxygen and carbon monoxide; he/she could make the presentation or discussion clinically relevant by using, as an example, a case of a family that sustained carbon monoxide poisoning from using a portable propane heater in their inadequately ventilated home (see case study 7 in Appendix C). The spectrum of morbidity among family members could be explained by referring to interactions with other risk factors, such as smoking, both active and passive, individual activity levels, and varying ventilation levels in the home. In the process, the instructor would be illustrating both the toxicologic concept that the risk level depends on the degree of exposure and the biochemical and physiological concept that oxygen is displaced from hemoglobin by a more avid binding agent. The differing fetal and maternal kinetics of carbon monoxide could be highlighted in this case, as could the pharmacologic principles of oxygen therapy and its hazards, and the neurotoxic effects of prolonged hypoxia.

> Carbon monoxide is the leading cause of poison-induced deaths in the United States (Centers for Disease Control, 1982).

The appendixes contain numerous other examples for incorporating environmental (including occupational) content into basic science teaching. The underlying principle guiding the use of such examples in the basic science curriculum is the need for a greater emphasis on clinically relevant examples. In those schools with a problem-based learning track, it is somewhat easier to incorporate environmental and occupational issues into the curriculum. Most cases can be written to include information on environmental and occupational risk factors that are either directly relevant to the learning issues of the case or are incidentally related to them without necessarily affecting the case.

Introduction to Clinical Medicine Courses

Some courses naturally lend themselves to teaching important concepts in environmental and occupational medicine. For example, "Introduction to Clinical Medicine" courses provide specific opportunities for introducing information on disease-exposure relationships and could easily emphasize environmental and occupational exposures. A discussion of the work-up and management of a patient with suspected interstitial lung disease, for example, which is fairly generic in its approach, could involve a patient with hypersensitivity pneumonitis secondary to exposure to pigeon antigen. Although the clinical work-up is initially similar for all patients with suspected interstitial lung disease, the specific work-up and diagnosis would clearly be dependent on an accurate environmental history and an understanding of the frequently misunderstood pathophysiology of hypersensitivity pneumonitis. It would then be important to compare distinguishing aspects of this condition with other interstitial diseases such as sarcoidosis, asbestosis, and idiopathic pulmonary fibrosis. In addition, a discussion of environmentally focused preventive measures can also be introduced as a corollary to medically oriented treatments such as oxygen and steroids.

> Exposure to allergenic bioaerosols in residential or commercial heating, ventilation, and air-conditioning systems can cause hypersensitivity pneumonitis (Institute of Medicine, 1993b).

Competency 3

Competency 3. **Graduating medical students should be able to elicit an appropriately detailed environmental exposure history, including a work history, from all patients.**

Introduction to Clinical Medicine/Medical Interviewing and Problem-Solving Courses

Introduction to clinical medicine/medical interviewing and problem-solving courses are the most logical place for teaching the skill of environmental and occupational history-taking. Environmental and occupational exposures can be considered important risk factors in what is often called the "social" history, which generally elicits information about a patient's life-style risks. Several strategies can be used to include and enhance students' environmental and occupational history-taking skills. For example:

Patient Write-Ups. Detailed environmental and occupational history and exposure information can be a required component of the patient write-ups that students are typically asked to submit.

Role-Playing. It may be interesting and useful to have students take histories from each other. Environmental and occupational exposure issues will likely surface as a result because some students will have encountered potentially hazardous environmental exposures through their hobbies, home and community environments, previous employment, or medical training (e.g., formaldehyde used to preserve specimens in the anatomy labs).

Standardized Patients. Patient-instructors are used increasingly to train students in the skills of interviewing, communication, and physical examination. Environmental and occupational elements can be easily added to these patients' scripts or scenarios. Indeed, the use of standardized patients to teach and evaluate history-taking skills should routinely require the elicitation of relevant environmental and occupational history and exposure data.

Computer-Based Learning. A variety of interactive computer programs have been developed that focus on clinical problems in environmental and occupational medicine, and these problems can be used to enhance students' environmental and occupational history-taking skills. Students can work through computer-based cases, which can be loaded onto the computers generally used by them. Because the development of sophisticated computer-based instruction takes time, money, and considerable expertise, faculty are encouraged to identify and use existing resources.

Written Material. Students may be more inclined to remember to include environmental and occupational information in their history-taking if they understand the relevance and importance of the exercise. Several excellent journal articles, some based on actual cases, are available and can be assigned as required reading. The ATSDR case study on "Taking an Exposure History" (see Appendix A) is a good example that can also be used. Additionally, written history and physical examination forms can be modified to specifically require the elicitation of environmental and occupational exposure information (Box 6 provides an example of the importance of history-taking).

Clinical Clerkships

Although history-taking skills are generally first taught in medical interviewing and introduction to clinical medicine courses, history-taking competence is developed over time outside the classroom during encounters with patients. Faculty interest, awareness, and reinforcement are critical elements in ensuring that environmental and occupational history-taking skills are practiced, developed, and maintained. In clinical clerkships, this can occur in a variety of ways.

Box 6. Acute Lead Poisoning

A 46-year-old white male with a history of appendectomy at age 12 and partial small bowel obstruction at age 37 presented to the emergency room with cramping abdominal pain radiating to his back which gradually had appeared and worsened over one week. He also complained of nausea, headache, fatigue, and aches in his forearms and wrists. He denied diarrhea or constipation. Physical exam was benign at the time, and the KUB showed a nonspecific gas pattern, so the patient was sent home with analgesic medication. Ten days later he returned to the E.R. with continued symptoms and constipation. Again he was sent home with analgesics and a laxative; follow-up exams included a barium enema and an upper GI series with small-bowel follow-through, both of which were normal. He returned two more times with steadily worsening pain and constipation. On the fourth visit his abdomen was notably tender to palpation and there were decreased bowel sounds. The patient went on to receive an abdominal CT scan and finally an exploratory laparotomy before any of the medical staff queried him on his hobbies.

The patient had recently purchased a 150-year-old house, which he was renovating completely. He was sanding the paint by hand, wearing a simple dust mask, and living and eating in the areas where he was working. His blood lead level was 130 μg/dl.

Lead poisoning is an important cause of abdominal pain and is not uncommon among painters and people renovating homes. The mechanism is thought to be neuropathic, and is characterized by a diffuse cramping in the presence of a fairly benign physical exam. Lead poisoning should always appear in the differential diagnosis of abdominal pain: it can save unnecessary tests and even unnecessary surgery.

Adapted from a case presented by Rose Goldman, M.D., M.P.H. during Occupational Medicine Grand Rounds at the Harvard School of Public Health on 10/8/93.
See also case studies 18 and 19 in Appendix C.

Morning Report. Attending physicians can emphasize and reinforce the importance of environmental and occupational histories and exposures by routinely asking students about them during morning report. They can also use the cases presented to encourage further learning about environmental and occupational exposures and health effects.

Conferences. Residency programs hold conferences for their house staff, which rotating medical students normally attend. Again, case-based discussions can stress the importance of environmental and occupational histories and exposure information in contributing to the differential diagnosis, treatment, and management of patients.

Site Visits. The relevance of understanding a patient's living and occupational environments can be enhanced by requiring students to visit a patient's home, workplace, or neighborhood. Site visits allow students to observe and experience their patients' living and working conditions in a way that is not possible in the office or hospital setting, even with a good history. One experience in a blatantly unhealthy environment or an industrial facility can make a lasting impression on students. This strategy may be easier to use in ambulatory clerkships.

Written Material. At the beginning of each clerkship, students can be given a list of conditions or presenting complaints frequently encountered during the clerkship that may be environmentally related. They can be told that they will be specifically evaluated on the environmental and occupational histories taken from patients with those conditions or complaints. Examples include dyspnea, chronic fatigue, pulmonary fibrosis, poor school performance, and skin rashes.

Competency 4

Competency 4. **Graduating medical students should be able to identify and access the informational, clinical, and other resources available to help address patient and community environmental health problems and concerns.**

Information about resources can be provided in almost any setting, including clinical clerkships. Some examples follow (see also Appendix D).

Written Information

Written materials that supplement and illustrate the clinical relevance of basic science concepts can include information on resources. For example, a clinical correlation on lead poisoning used to supplement material on heme synthesis can include information on the Centers for Disease Control and Prevention (CDC) guidelines, federal, state, and local agencies with toll-free hotlines, the name and telephone number of the medical school's expert on lead poisoning, and sources of patient education material on lead. Similar types of "resource sheets" can be developed to provide information to students in their clinical clerkships. These resource sheets can focus on the types of problems or issues frequently encountered in a specific clerkship. For example, for a clerkship in family medicine, a resource sheet on indoor air contaminants would be useful to help parents of asthmatic children or patients with concerns about the air quality in their homes or workplaces.

Community Placements

Students can be placed with agencies, organizations, or specialists that deal with environmental and occupational issues in a longitudinal or block manner to enhance their understanding of these issues and the role of community resources in addressing them. Possible placement opportunities include state and local health departments and environmental agencies; environmental advocacy groups; local industry; labor unions; local chapters of cancer, heart, and lung societies; poison control centers; and environmental and occupational medicine specialists' practices. These types of placements may be possible during community or preventive medicine courses, as well as during the summer between the first and second years. They can also form the basis of electives in environmental or occupational medicine for students with special interest in the field.

Problem-Based Learning, Clinical Precepting

In working up or reporting a case with a possible environmental connection, preceptors and attending physicians can ask students to obtain additional information or assistance. For example, an attending physician (or resident) could direct a student to identify and call a local expert in lead neurotoxicity; they could be told to investigate the health effects of a particular substance; or the small-group preceptor could suggest that students investigate the availability of local resources and determine what these resources can provide.

Competency 5

Competency 5. **Graduating medical students should be able to discuss environmental risks with their patients and provide understandable information about risk-reduction strategies in ways that exhibit sensitivity to patients' health beliefs and concerns.**

Communication Skills and Interviewing Courses

In courses that use simulated patients to help teach communication and interviewing skills, the patients can be instructed to display various degrees of concern about potential environmental exposures. Evaluation and feedback can include commentary on a student's listening and counseling skills and their sensitivity to the patient's concern about environmental exposure(s). The student can be expected to validate the patient's concern, avoid the temptation to dismiss the environmental concerns in favor of a focus on life-style risk factors, avoid making the patient's fear or concern seem irrational, and explain the degree of uncertainty inherent in medical risk assessment.

Epidemiology and Preventive Medicine Courses

Lectures and Supplementary Written Materials. Environmental and occupational factors can be easily included when teaching students how to characterize risk and identify preventive measures to reduce both population and individual risks. Journal articles that report epidemiologic studies of environmental and occupational diseases can be used to stimulate discussion of prevention and risk reduction (see Box 7). Handouts can be prepared that familiarize students with the range of risk-reduction strategies applicable to environmental and occupational hazards, from environmental modification to the provision of personal protective equipment and medical screening programs.

Workshops and Small-Group Sessions. Students can discuss environmental and occupational risk-reduction strategies and practice their counseling skills in small-group workshops that use cases, clinical problems, or role playing.

Basic Science Courses or Problems

Sessions or written materials used to supplement basic science concepts can include information on appropriate risk-reduction strategies. For example, a clinical correlation to basic science material on allergen-mediated asthma and anaphylaxis could address the issue of latex allergy in hospital workers and provide information on possible risk-reduction strategies, such as the use of nonlatex gloves. Similarly, a clinical correlation to basic science material on heme synthesis could address ways to reduce lead exposure among children or bridge painters.

> Dust from latex gloves is a significant occupational aeroallergen (Institute of Medicine, 1993b).

Clinical Clerkships

Preceptors can be encouraged to require students to ask and counsel patients about workplace and environmental risks. Students can then be observed and evaluated on this skill.

Box 7. Methylmercury Poisoning (Minamata Bay)

A 14-year-old boy living in a small city in Japan went to a local hospital in July of 1958 with recent onset of a number of neurological symptoms. He had numbness around his mouth and in his hands and feet; he was also increasingly clumsy and had difficulty buttoning his clothes and handling his chopsticks. Over several weeks he developed a staggering gait and became increasingly deaf. He also had a diminished attention span. At no time did he have a headache, fever, or stiff neck.

On physical exam he was markedly ataxic and dysarthric, his behavior was inappropriate to his age, and he had excessive salivation. The boy's visual fields were constricted peripherally, through fundoscopic exam, and eye movements were normal. There was no nystagmus and muscle strength was normal. Reflexes were slightly diminished, more on the left than the right. Babinski was positive on the left and negative on the right. An unintentional tremor was present, and finger-to-nose and heel-to-shin tests were both abnormal.

The boy was one of over a hundred people struck by acute methylmercury poisoning after eating fish caught in Minamata Bay. A nearby vinyl chloride production plant had been dumping untreated chemical waste into the bay for years. The mercury in the waste made its way into the food chain, finally reaching concentrations sufficient to cause acute poisoning in those who consumed fish from the bay. Methylmercury primarily affects the central nervous system. Post mortem examination on fatal cases revealed cerebral edema, cerebellar atrophy, and diffuse cellular degeneration particularly in the granular layer of the cerebellum. Today mercury is found in some fungicides, disinfectants, some industrial cites, and (in low concentrations) in seafood throughout the world.

Adapted from Kurland et al. (1960).
See also case studies 21 and 22 in Appendix C.

Competency 6

Competency 6. **Graduating medical students should be able to understand the ethical and legal responsibilities of seeing patients with environmental and occupational health problems or concerns.**

Ethics Courses

Although not typically covered in ethics courses, the ethical dimensions of identifying, managing, and preventing cases of environmental and occupational disease can be discussed, as can physicians' legal responsibilities. For example, cases or journal articles can be used to illustrate and discuss physicians' ethical responsibilities for reporting serious environmental and occupational problems dealing with suspected hazards, protecting confidential information, and handling conflicting responsibilities to patients, employers, insurers, and others.

Community and Preventive Medicine and Public Health Courses

Courses in community and preventive medicine and public health provide opportunities to introduce students to legal and ethical concepts relating to environmental and occupational health. For example, community laws relating to waste disposal, recycling, or smoking in public places can be discussed, as can state and federal disease reporting laws, and toxic substance exposure registries.

Clinical Clerkships

Legal and ethical issues most frequently arise in the course of patient care, so the clinical clerkships are some of the best avenues for making students aware of their legal and ethical responsibilities. These types of issues commonly arise in the context of workers' compensation, disability evaluations, return-to-work notes, incidents of environmental contamination (e.g., Love Canal), or an acute exposure to a toxic substance.

Conferences

Clinical case conferences, and even Grand Rounds, are excellent vehicles for raising the legal and ethical issues inherent in many environmental health problems. When presenting or discussing a clinical case involving environmental or occupational exposures, faculty can incorporate the legal and ethical elements, thereby highlighting the inseparability of these issues.

Love Canal, New York is the site of one of the most well-known community hazardous waste stories in the United States. During the 1940's, approximately 22,000 tons of chemical manufacturing wastes containing dioxins, polychlorinated biphenyls, and other hazardous compounds were dumped and later buried in the canal. Later, a housing development was built on the site, and in the 1970's, residents began to notice unusual odors and oily puddles around their neighborhood. The federal government declared the site a disaster area and removed the residents from their homes (Upton and Graber, 1993).

Standardized Patients

Use of standardized patients would be ideal for helping students become more effective communicators within a context that, depending on the patient and the case, is sensitive and laden with socioeconomic, ethical, and legal issues.

ENHANCING FACULTY AWARENESS

As noted at the beginning of this chapter, any effort to integrate environmental health into the medical school curriculum requires faculty interest, commitment, and competence. Because the existing pool of medical school faculty with expertise in environmental medicine is exceedingly small, both long- and short-term strategies for expanding basic and clinical science faculty resources in this area must be pursued.

Some Long-Term Strategies

In the long term, more young scientists and physicians must be recruited into the area of environmental medicine. To develop a basic level of competence in all medical school and residency program graduates, the number of role models on the faculty must be expanded. As in other disciplines, possible incentives in environmental health are both economic and non-economic in nature. The field must be attractive, providing both personal satisfaction and economic opportunities to those who pursue it, and individuals must be made aware of the field and its potential for professional growth, development, and economic opportunity. Throughout their years of undergraduate education, students must be nurtured and encouraged to pursue their interest in the environment. In years K-12, there are now initiatives to develop students' environmental awareness and literacy. At the college level, faculty could build on this awareness in their courses and in the counseling they do with pre-med students and students interested in pursuing graduate degrees. Nursing schools and other health profession training programs can introduce students to career opportunities in environmental health. After college, adequate training support and stipends would make it easier for medical students and residents to pursue advanced training in occupational and environmental medicine, as would environmentally-focused research fellowships and traineeships for graduate students in the basic sciences. Beyond this, however, these newly trained professionals must be assured of continued support for their environmental health research and teaching activities. If this support is lacking, new faculty members will have considerable difficulty sustaining their work in the field. Thus, the committee strongly supports the recommendations for expanding environmental health research made by the IOM in 1988 (Institute of Medicine, 1988), as well as expanding environmental health teaching activities. Expanding research, education, and training becomes more important as we witness the continued pollution and degradation of our environment and experience the increasing public concern about possible related health effects.

Some Short-Term Strategies

Despite its importance, we need not wait until an expanded cadre of experts in environmental medicine is in place to begin integrating an enhancement of environmental medicine into medical education. Most medical schools already have faculty with at least some expertise in environmental medicine and who would be interested and willing to assist. Thus, a helpful short-term strategy would be to identify such a person who could serve as a champion for environmental medicine in the school and among the faculty. In schools with existing programs or expertise in environmental or occupational medicine, this champion may be easily identified. In schools without existing programs, this champion may be a respected teacher or clinician, prominent investigator, or activist in curricular reform from any discipline or department. The champion may also be a faculty member who has a personal interest in the environment because it directly or indirectly relates to his/her area of research, or because he/she has a personal concern about the environment—be it preservation of the environment or protection of human health. If not champions, these same individuals may serve as important allies in any effort to integrate environmental medicine into the curriculum. Because environmental health covers a wide range of topics—from toxic substances and infectious agents to particular diseases, population growth, and family planning—most medical school faculty will already have some knowledge and/or interest within their own disciplines about environmental factors and related medical conditions. This knowledge and/or potential interest in environmental and occupational health should be identified (perhaps as part of the inventory described at the beginning of this chapter) and nurtured by encouraging faculty to incorporate an environmental medicine focus into the courses and clerkships they teach.

Among basic science faculty, an opportunity to nurture this interest may lie in an increasing concern with making courses more clinically relevant as a way to enhance long-term learning as well as course satisfaction among medical students. In the process of modifying the basic science curriculum, for example, a champion with expertise in environmental and occupational medicine could review course syllabi and materials with course directors to identify possible access points within the course that would be amenable to and enhanced by introducing environmental and occupational medicine issues. With some assistance and without too much effort, the course director could then incorporate clinically relevant material, as well as opportunities to discuss prevention strategies, in lectures or small group problem-solving sessions. As illustrated in Appendix B, this integration can occur in almost every basic science discipline.

These same faculty can be encouraged to pursue the environmental connections in their own research, especially if sources of support can be identified. There is no paucity of research needs in this area, and the potential for interdisciplinary collaboration is substantial.

Among clinical faculty, efforts to increase the knowledge of, and/or interest in, environmental and occupational medicine can take several forms, but the fundamental appeal should be to assist them in responding to patients' questions about environmental hazards, counseling them appropriately, and providing effective treatment. With increasing public concern about the environment, physicians more frequently encounter patients with questions about potential exposures, or symptoms that patients attribute to occupational or environmental conditions. Thus, clinical faculty may find it in their interest to learn more about these issues so they can adequately address them in their practice and in their teaching. This can be accomplished, in part, through presentations at departmental conferences and rounds, formal faculty development programs, the development and provision of brief, clinically relevant teaching materials for use in specific clerkships, and personal mentoring of interested junior faculty. Additionally, faculty with expertise in occupational and environmental medicine can serve as educational role models—perhaps offering to attend an occasional morning report or afternoon case rounds.

Clinical faculty, especially junior faculty, may seize on the opportunity to develop themselves as institutional or local resources in environmental health for their clinical colleagues. This may enhance their prestige in the community and among students who may more fully appreciate the importance of the environment to human health. Of course, this may require institutional support for these faculty members to develop their own competence.

The single clinical skill the committee views as the key component of an environmental medicine curriculum is the ability to obtain a meaningful environmental (including occupational) history. As with any clinical skill, its elements must be specified, demonstrated, practiced, and reinforced by faculty who are comfortable and experienced in its uses. Efforts to encourage faculty to focus on this skill should be aimed at those

Students should be made to realize from the beginning of their clinical studies that the diagnosis in a large majority of illnesses can be made on the basis of a searching history, a thorough physical examination, relatively simple laboratory determinations, and the thoughtful consideration of the problem presented (Rappeleye, 1932).

involved with precepting in ICM (Introduction to Clinical Medicine) courses and at faculty preceptors in clinical clerkships, whether they are hospital or community based (see Appendix B, ICM Section). In either case, guidelines for faculty could include information on taking an environmental and occupational history, with an explanation of why and how each element of the history is useful and important for arriving at a diagnosis or developing a clinical plan of action. The guidelines can be developed around an example of a common patient complaint in a particular discipline to better illustrate the relevance of the environmental and occupational history to the practitioner. The guidelines could also include samples of environmental/occupational history forms, checklists, or formats for evaluating students' history-taking skills (Appendix A contains the ATSDR case study on "Taking an Exposure History," which is a good example). In those schools that hold orientation sessions for precepting faculty, a standardized patient could be presented to illustrate the way an environmental and occupational history should be taken. Alternatively, preceptor orientation could include written materials and one of several existing videotapes that demonstrate how to take a sufficiently detailed history in a given clinical setting.

In general, efforts to enhance faculty awareness of environmental medicine should focus on those who teach and practice primarily in ambulatory settings, particularly those with a primary care practice. Because information and resource issues are relevant only when faculty are faced with a clinical problem, problem-solving approaches should be the mainstay of this effort. Illustrative examples can be prepared and distributed to preceptors, along with concise descriptions of key agencies, organizations, and professionals easily accessible by telephone, that can provide appropriate and timely information in the evaluation and management of patients with potential environmental exposures or illnesses. As a first step, faculty could be informed of the broad-based information currently available on environmental exposures at most nationally certified poison control centers.

Many clinical faculty lack the skills needed to counsel patients about environmental and occupational risks. As a result, those serving as preceptors might be hard pressed and perhaps uncomfortable in demonstrating these skills or supervising students in their patient encounters. In such cases, standardized patients, role-playing, dramatized presentations, and videotapes, alone or in combination, can be used to raise faculty competency. Clearly, the medium and the educational setting are dependent on the organization and resources available to those responsible for ensuring appropriate faculty supervision of student education.

Finally, it should not be forgotten that students can affect faculty awareness of issues. For this reason, we need innovative ways to capitalize on student interest in the environment and health extracurricularly. For example, schools could support the establishment of environmental health student interest groups that might initiate environmentally related activities (e.g., recycling programs at the school) or host other events with invited speakers. Schools and agencies could identify and support summer internships and student research projects in environmental medicine. Such student initiatives would influence faculty awareness and help engender enthusiasm that could affect changes in the curriculum.

CONCLUSIONS AND RECOMMENDATIONS

Fundamental to the recognition, evaluation, and resolution of environmentally related illness and injury will be the availability of informed physicians who understand the relationship between the environment and health and who can provide care and counsel to their patients and their communities potentially at risk for, or already affected by, environmentally related illness and injury. Achieving this level of competence will require the development and delivery of educational programs that give physicians the knowledge, skills, and attitudes needed to deal effectively with environmental factors in both clinical and public health contexts.

The strategies for integrating environmental medicine into medical education proposed in this report are economical as well as effective. They require no new curriculum time and few, if any, additional resources.

Integrating the Curriculum

Environmental medicine may already be addressed in unexpected places in the curriculum. Thus, it will be helpful for medical schools to inventory the content of their educational programs throughout the four years of medical education and assess their relevance to the objectives suggested in this report. Where deficiencies exist, materials such as those presented in this report can facilitate and enhance the integration of environmental medicine concepts. The needed instructional materials and basic concepts can be included in existing lecture series, as part of existing courses, or as supplements in problem-oriented case discussions. The establishment or enhancement of this content in the school's curriculum may also facilitate efforts to integrate the basic and clinical sciences, as well as helping to promote stronger relations between the medical school and the community in which it resides.

The actual content used to help students develop the six competencies will vary, reflecting faculty interest and expertise, student interest, the conditions and risks in the local community, and institutional resources and constraints. Some students will develop these competencies by learning about heavy metals, while others may apply them to cancer or respiratory diseases. In all cases, the underlying goals should be the same—to teach students about causation, history-taking, and disease prevention.

Developing Faculty

In order to ensure adequate attention to environmental medicine in medical education, an enhanced awareness of the importance and integral nature of environmental medicine is needed among all faculty, as well as an increase in the number of medical school faculty with expertise in environmental medicine. The committee supports previous IOM reports that noted a severe shortage of such personnel and made recommendations for increased funding to support faculty development (Institute of Medicine, 1988; 1991).

The development of faculty as educators in environmental medicine requires more than simple encouragement to integrate the topic into their teaching. Faculty need to understand the relevance of environmental medicine to patient care, to the health of the public, and to their own disciplines. They need concrete examples of innovative and interactive materials and methods for incorporating environmental medicine into their teaching without significantly increasing their time commitment. They also need colleagues in their own and other disciplines to share their commitment to and enthusiasm for creating an environmental focus in their courses and teaching programs. Professional associations and organizations can and should play an important role in advancing this interest in environmental medicine. Position papers on the relevance of environmental medicine to their particular disciplines or specialties would be helpful in this regard, as would articles in their journals that emphasize the critical relationship between environmental health and physician involvement.

In addition, faculty should be encouraged, supported, and rewarded for their teaching activities—in this case, their teaching of environmental medicine. Establishing awards for innovative teachers/educators is one mechanism. Other possibilities include short-term faculty internships/projects and the development and implementation of traveling faculty development programs. Federal support for such programs should be established within the Department of Health and Human Services and the Environmental Protection Agency.

Because what is learned in the classroom must be reinforced in the clinical setting, it should be made easy for clinical faculty to routinely consider environmental and occupational factors in their patient care activities. Many things are needed to facilitate this including: making environmental history-taking reimbursable; developing usable forms and data systems; establishing a quick source of information and/or referral

> Experience indicates that the commitment to education of deans and departmental chairmen greatly influences the behavior of faculty members in their institutions and their departments. By their own attitudes and actions, deans and departmental chairmen should elevate the status of the general professional education of medical students to assure faculty members that their contributions to this endeavor will receive appropriate recognition (Association of American Medical Colleges, 1983).

resources; and expanding continuing medical education activities in this area.

Continuing Education

At the outset the committee restricted its discussions and recommendations to undergraduate medical education, but it soon became apparent that environmental and occupational medicine should be a part of the full continuum of medical education, including postgraduate training and the continuing education of practitioners. To the extent that medical schools assume responsibility for the continuum of medical education, environmental and occupational education should be a part of their overall curriculum. Efforts to enhance medical practice by integrating the six competencies into continuing education should be expanded, with appropriate emphasis on community issues.

Many important, continuing medical education initiatives in environmental medicine are currently available or in development. The American College of Occupational and Environmental Medicine, for example, has developed a comprehensive, 18-hour environmental medicine curriculum that can be adapted to a variety of educational formats. This curriculum course is offered to interested participants at their annual meeting. The Agency for Toxic Substances and Disease Registry has supported the development of a course in pediatric environmental health (California Public Health Foundation, 1992), as well as a series of case studies in environmental medicine (see Appendixes A and C). Innovative educational methodologies have been developed by recipients of Preventive Pulmonary Academic Awards given by the National Heart, Lung, and Blood Institute. The National Institute of Environmental Health Sciences' Environmental/Occupational Medicine Academic Award recipients are developing educational materials and methodologies and history-taking techniques to facilitate the integration of environmental and occupational medicine into the medical school curriculum. A list of medical schools that currently receive these awards and have available expertise and information in environmental medicine appears in Appendix D (see pages 917-918 and 920). These activities, and others like them, have been very useful in the development and integration of environmental medicine concepts and materials into medical education. Continued support for these activities is needed and should be expanded if possible to help ensure the enhancement of environmental medicine in medical education. Expansion activities should include establishment and support of: (1) an environmental medicine speakers bureau, with speakers who can address the concerns and issues of specific disciplines, e.g., pediatrics, obstetrics, neurology, etc., and (2) a database of curricular materials and activities for use by faculty and students.

Evaluating Progress

Even when undertaken with the best of intentions, curricular reforms can easily become more symbolic than substantive if they are not "kept honest" through careful evaluation. The committee strongly recommends that medical schools develop a plan for evaluating their progress in implementation as they begin to integrate environmental and occupational medicine into their curricula. The evaluation plan should be a serious part of the overall effort, not an afterthought. In some cases, it may be possible to develop a rigorous plan for systematic evaluation, possibly with outside technical assistance; in other cases, the evaluation will be more informal. Either way, a genuine commitment is vital to check up on the innovation as it proceeds.

The curricular changes recommended here must necessarily be tailored to each medical school's particular circumstances. In addition, in each school the effort is likely to go through considerable evolution before stabilizing, with trial and error around specific changes. Therefore the approach to evaluation should be a comprehensive, flexible one that includes both process evaluation and impact assessment. The "process" part of the evaluation plan should include (a) needs assessment aimed at understanding the context into which the changes must fit, and (b) program monitoring aimed at tracking the implementation of the changes. The "impact" part consists of effectiveness studies aimed at measuring the program's success in meeting its objectives. At a later stage, it might also be appropriate to undertake some efficiency studies to determine the most cost-efficient ways of effectively delivering training in environmental medicine.

For needs assessment, some useful focal points for examination include the following:

- An inventory of environmental medicine content already available in courses and related clinical training.
- Identification of faculty expertise in environmental medicine, broadly defined.
- Assessment, through surveys or focus groups, of the faculty's receptivity to the proposed innovations. Are they interested in the new material? Do they feel competent to teach it? Are they willing to teach it? Do they want to modify or extend it? Can they suggest any special faculty training or support needs, any barriers to change that could be removed, any incentives that could be offered?
- Assessment, through surveys or focus groups, of students' interest in the proposed

innovations. Do they recognize a need for this training, or do they regard it as an unwanted extra? What training format would work best from their perspective?

- Assessment, through surveys or focus groups, of commitment to the proposed changes on the part of the school's leadership. How enthusiastic are they about the changes? Do they anticipate any problems in implementation? How much tangible institutional support will they give to the curricular changes being proposed?
- An inventory of relevant local resources and opportunities for community placements, interdisciplinary connections, and inter-institutional cooperation.

For program monitoring after some of the changes have begun to take effect, two levels of program operation should be examined: (a) the system of delivering the new training, and (b) patterns of participation in the new training. At the first level, the task is to document exactly what new content is being offered and through what mechanisms it is being provided. At the second level, the task is to analyze what part of the student body is being exposed to the new training, and which faculty are involved in delivering it. Since the actual program operation may differ from the intended program operation, the monitoring data should wherever possible be collected through direct observation and inquiry rather than from documents that describe what ought to be happening. The monitoring effort should include some open-ended exploratory data-gathering in order to detect unanticipated developments or problems. To provide useful program oversight, program monitoring should ideally be carried out at least once a year.

To evaluate program effectiveness (or "impact"), a central concern would be the measurement of student performance on the six competency-based leaning objectives described in this report. The simplest but methodologically weakest approach is simply to assess the extent to which graduating students demonstrate the six competencies. This establishes that they know the desired content, but not necessarily that they learned it as a result of the training provided, since they could have had these competencies all along, or developed them through experiences outside the program. The case for program effect could be strengthened by adding a "before" measurement of the six competencies among incoming students, to be compared with an "after" measurement at the point of graduation. An even stronger case for program effect would come from an evaluative study with experimental design, in which before-after competency measurements for students receiving the environmental medicine training are contrasted with comparable measurements for a control group that does not receive the training. Because practical constraints often make experimental design infeasible, setting up a valid effectiveness study can be a real methodological challenge. Fortunately, a variety of quasi-experimental designs have been worked out to approximate the logic of experimental control in evaluating program effectiveness. These are described in numerous readily available texts on evaluation research (Cook and Campbell, 1979; Patton, 1990; Rossi and Freeman, 1993; Schalock and Thornton, 1988).

Evaluating medical students' competencies in environmental medicine at the point of graduation is clearly very important. But will the graduates retain these competencies over time? The long-term effect is much harder to evaluate. One approach, supported by this committee, is for the National Board of Medical Examiners and the Federal Licensing Examination to incorporate into their certifying examinations the six competencies described in this report.

Probably the most meaningful way of evaluating program effect would be to assess medical graduates' actual use of the six competencies in their post-graduation practice. Are they finding it possible to put their environmental medicine training into practice—and if not, why not. This kind of assessment, which might be done through a survey of graduates, could be carried out only after the training had been in place for some time.

Other potential program effects that might be examined in individual medical schools include changes in faculty attitudes, activities, and competencies related to environmental medicine; changes in administrative awareness and support for environmental medicine; and changes in the medical school's patient services and community activities related to environmental medicine.

4

Changing Medical Education

There is a growing consensus among medical educators in North America that both the content and structure of medical education require fundamental change (Anderson, 1993; Marston and Jones, 1992; Morris and Sirica, 1992; Pew Health Professions Commission, 1991). Despite this recognition, meaningful and sustainable change continues to be difficult to initiate. This chapter outlines the general nature of change in medical education and specific aspects of introducing environmental medicine into the medical school curriculum.

CALLS FOR REFORM IN MEDICAL EDUCATION

The integration of environmental medicine into the medical school curriculum fits nicely with recent calls to reform medical education. Over the past decade, numerous organizations, commissions, and foundations have proposed initiatives to reform the process, content, and structure of medical education in the United States (Enarson and Burg, 1992). A remarkable degree of consensus has emerged from these studies. In its own way, each report emphasizes the need for medical schools to place students at the center of their missions, and each urges the schools to prepare their students to meet the changing health care needs of the American public (Association of American Medical Colleges, 1992a). In characterizing the future U.S. health care system, the Pew Health

Professions Commission projected a system that would be more oriented on health, would stress disease prevention and health promotion, and would be population based to respond to the increasing attention paid to social and environmental risk factors (O'Neil, 1992; Pew Health Professions Commission, 1991). In this context, the Pew commission articulated a responsibility for health professionals to understand, maintain, and improve community health and thus the need for future physicians to understand the societal and environmental determinants of health. Other studies have noted the need to shift the focus of medical education from acute to chronic conditions and from an infectious to a biopsychosocial model of health and disease (Association of American Medical Colleges, 1992a).

Many of the reform proposals pose opportunities for integrating environmental medicine into medical education in the sense that: environmental medicine is responsive to the calls for cross-disciplinary teaching; environmental medicine melds basic and clinical science and reinforces the basic and biomedical sciences throughout the course of medical study; it moves training away from tertiary-care teaching hospitals and into the community; and it emphasizes student-directed, problem-based learning (Association of American Medical Colleges, 1992a,b; Marston, 1992; O'Neil, 1992). Environmental medicine is also central to primary care.

Despite the plethora of studies, reports, and recommendations, however, actual efforts to respond to the calls for change have been less than noteworthy and successes have been few (Anderson, 1993; Enarson and Burg, 1992). There is, nonetheless, a steady and growing interest among medical schools in reform, presenting a window of opportunity for environmental medicine. The key to seizing this opportunity is realistic implementation strategies for importing knowledge about the environment and its role in health into mainstream medical education. Chapter 3 of this report described some potentially effective implementation strategies; the remainder of this chapter describes potential barriers and opportunities that may be encountered in attempting to modify medical school curricula.

BARRIERS AND OPPORTUNITIES

For decades, the basic structure of the medical school curriculum has changed very little. Medical school curricula, although superficially varied, are designed to prepare students for graduate medical education and practice. The four years of medical school are commonly divided into two years of discipline-oriented preclinical (basic science) studies followed by two years of clinical studies. Clinical education has traditionally occurred in the hospital, although students increasingly learn in outpatient, ambulatory care facilities. At many medical schools, the fourth year is primarily student-designed, and students spend much of their time in elective study. This period also involves time spent interviewing for future residency positions. To the extent that the preclinical and clinical programs are temporally distinct, the integration of basic sciences with their clinical application is less than ideal.

In response to concerns about traditional medical curricula, innovative new programs of undergraduate medical education have emerged within the past decade (Anderson, 1993). The content and structure of some of the new programs share some common features, each of which is relevant to an environmental medicine curriculum:

- more interdisciplinary courses that integrate basic and clinical sciences—an opportunity easily realized in environmental medicine;
- an emphasis on the mastery of biological concepts;
- content related to social and behavioral aspects of health and disease; and
- ambulatory and community clinical experiences that teach health care organization, practice, and financing.

In addition, some of the new programs include experiences with problem-based learning and small group interactions with faculty, as well as more independent learning. While reports suggest that many medical schools are considering similar programs and some schools have already made significant changes in their curriculum, such change is far from universal. The majority of North American medical schools continue to use traditional programs, whose entrenchment is deep and resistant to modification.

Even though the shortcomings of medical education have been identified and widely acknowledged for many years, several barriers appear to obstruct schools from making the changes they agree should be made. Some of these barriers are likely to be encountered by advocates for environmental medicine.

Barriers

Over the years, there have been many calls for curriculum reform, but structural barriers have hampered progress (Anderson, 1993). Medical education is still largely dictated by and compartmentalized into departments and disciplines, generally focused on information transfer rather than problem solving, reliant on traditional teaching methods, and overwhelmed by an ever-expanding knowledge base.

In a report entitled *Educating Medical Students: Assessing Change in Medical Education—The Road to Implementation*, also known as the ACME-TRI report (Association of American Medical Colleges, 1992b), the Association of American Medical Colleges assessed the degree of change in medical education and identified barriers to successful change. The five most prominent obstacles found were:

1. a lack of oversight for the educational program;
2. limited resources and no defined budget for medical students' education;

3. faculty inertia and a lack of incentive for faculty to teach;
4. lack of leadership in the educational program; and
5. lack of evidence that implementing the suggested changes will make the necessary improvements.

These barriers were identified repeatedly by respondents to the ACME-TRI project survey and represent key elements that must be altered, or overcome, if meaningful change is to occur in the medical school curriculum, including the integration of environmental medicine.

In any attempt to change the manner or content of instruction in medical schools, it is important to keep several realities in mind regarding time constraints and competing demands. First, the current academic reward system makes most members of the faculty reluctant, if not unwilling, to be involved deeply in teaching because it interferes with their academic careers. Despite the fact that interaction with students may well have been one of the most important factors in their choice of an academic career, most faculty members are under considerable pressure to seek research support, carry out research, and generate publications to support their progress up the conventional ladder of academic success. Second, those in clinical departments are required to generate much of their compensation through patient care. Third, all faculty participate in myriad, time-consuming committees and meetings for various academic, scientific, professional, and community causes. One of the key tasks for those committed to education is to establish a professional environment in which interested faculty members can implement new educational programs without adversely affecting their careers or penalizing their income or that of their department.

All the recent studies of change in medical education acknowledge that resistance to change is partly attributable to the institutional matrix of discipline-based departments in which most medical education takes place and that is characterized by the three realities described above. Bloom (1988, 1989) describes a "corporate-style bureaucracy" in which departmental and individual autonomy, resources, and prestige are organized around the research enterprise and, increasingly, revenue-generating clinical services. One of the statements in the ACME-TRI report sums up this problem as follows:

> . . . department chairs acknowledge that medical students' education is not a principal priority for their departments, . . . because of associated revenues and the importance of providing recognition for faculty members in their disciplines, [chairmen and faculty members] are more concerned with excellence in regard to graduate students, residents, research, and patient care. (Association of American Medical Colleges, 1992:3)

It is important to understand that virtually all academic chairmen over the age of 50 have reached their prominent positions through the very systems now subject to change. Further, these chairmen inherited tenured faculty members who have also risen to senior ranks in these same long-standing pathways, involving many hours of classroom exposure, many hours spent lecturing, and a habit of teaching facts rather than using factual information as a means of inspiring students to understand important concepts.

Indeed, the ACME-TRI study found that the major constraint to establishing a central administrative structure with the authority to plan and manage the medical education program is the unwillingness of faculty members in various departments to relinquish their authority to determine the knowledge and skills that medical students should acquire. This privilege is defended even when department chairs acknowledge that medical student education is not a principal priority of the department.

Proposals that involve the rebudgeting of funds and that provide a defined, centralized budget for medical student education also meet stiff resistance. However, pressure to develop central control could increase, especially with the accreditation standard set by the Association of American Medical Colleges' Liaison Committee on Medical Education that requires central curriculum management. The standard states that: "There must be integrated institutional responsibility for the design and management of a coherent and coordinated curriculum. The chief academic officer should have available sufficient resources and authority to fulfill this responsibility"(Liaison Committee on Medical Education, 1991). Thus, the Liaison Committee has an opportunity to be an agent of change if it chooses to interpret strictly its own standards and exercise its authority in this fashion.

Factors beyond the medical school itself also tend to sustain and reinforce traditional programs. Such factors include the dynamics of discipline-based scientific and medical societies, issues of public policy, and funding of education and health care. On some of these fronts, however, there are indications that the barriers may be coming down.

Opportunities

In the face of the barriers described previously, there are also some encouraging opportunities. This report describes three briefly: (1) an increased emphasis on prevention, (2) a paradigm shift in the knowledge base, and (3) a small but promising set of programs that support the development and integration of environmental medicine into medical education and practice.

Prevention and Future Health Care

The competency-based learning objectives set forth in Chapter 2 conform to several tenets underlying some of the current evolutionary trends in health care. Future systems of health care are likely to place more emphasis on the role of prevention and the need for accountability. In addition, the capacity of state and local public health agencies may be strengthened to help protect communities against communicable diseases and exposure to toxic environmental pollutants, occupational hazards, harmful consumer products, and poor-quality health care, as well as to inform and educate health care consumers and providers about their roles in preventing and controlling disease.

Responding to the evolutionary forces in today's health care system, professional groups have further emphasized the need for and clarified a taxonomy of prevention in health care to include personal or clinical preventive services, community-based preventive services, and social policies for prevention (Partnership for Prevention, 1993). Applying this taxonomy to environmental risks and disease, Table 1 illustrates the range of potential roles for physicians in environmental medicine (see also the discussion in Chapter 1), as well as the salience of the recommended competency-based objectives.

With or without substantial changes in the health care system in the United States, prevention is likely to play a larger role in the future practice of medicine, providing opportunities for the integration of environmental medicine into both education and practice.

Table 1. Some Examples of Components of Prevention in Environmental Medicine.

Personal or Clinical Preventive Services	Community-Based Preventive Services	Social Policies for Prevention
Taking environmental and occupational exposure histories, evaluating risk, and screening for detection of disease	Providing individual and community education about environmental conditions, risks, and workplace health and safety	Promoting regulatory policies to reduce environmental health hazards and increase work-place health and safety
Counseling individuals about environmental and occupational health risks and building the knowledge, skill, and motivation to avoid risks and maintain healthy life-styles	Evaluating and taking action to assure the availability of safe air, water, and food supplies, as well as healthy workplaces	Supporting and promoting economic incentives to encourage environmental protection, clean technologies, and pollution prevention
Intervening with chemoprophylactic agents	Providing outreach services to identify individuals or populations with environmental and occupational health risks and to link them with appropriate services	Advancing and supporting consumer product safety

SOURCE: Adapted from Partnership for Prevention (1993).

The Knowledge Base

Recent progress in medical science may facilitate educational change by directly affecting the knowledge base underlying medical education. Some educators assert that the unifying scientific concepts inherent in molecular biology represent a paradigm shift to an interdisciplinary knowledge base. In addition, new teaching methods and advances in medical informatics provide tools for integrating the multiple disciplines represented in medical instruction. Examples of these concepts and approaches are provided in Chapter 3 and the appendixes with respect to integrating environmental medicine into medical education.

Funding and Availability of Environmental Medicine Programs

There are several programs that support education and training, curriculum development, and research in environmental medicine, although funding is limited. A brief description of these opportunities is provided here, with additional details presented in Appendix D. Appendix D also lists the medical schools that currently receive support from these programs in order to assist the reader in identifying where to find expertise in environmental medicine (see pages 917-918 and 920).

Among the programs described in Appendix D are several sponsored by the National Institute of Environmental Health Sciences (NIEHS), one of the principal federal agencies for biomedical research on the effects of chemical, physical, and biological environmental agents on human health and well-being. These NIEHS sponsored programs include the Environmental/Occupational Medicine Academic Awards to medical school faculty members for improving environmental/occupational medicine curricula, and the Environmental Health Sciences Center Awards to universities for conducting multidisciplinary research in environmental health. NIEHS has established Basic Research and Education Programs to support research on preventing adverse human health effects of hazardous substances, and Hazardous Waste Worker Health and Safety Training Awards and Programs to support development and administration of programs for training workers and supervisors in health and safety. Clinical Investigator Awards are also available for the development of clinical investigators in the field of environmental health/human toxicology.

Another program described in Appendix D is Project EPOCH-Envi. This project, cosponsored by the National Institute for Occupational Safety and Health (NIOSH) and the Agency for Toxic Substances and Disease Registry (ATSDR), focuses on introducing curricula in occupational and environmental medicine into primary care residency programs. ATSDR also provides a self-study series called *Case Studies in Environmental Medicine* (many of which appear in the Appendixes of this report). These case studies guide physicians through the diagnosis and treatment of illness related to hazardous environmental exposures. They are useful teaching aids and can also be completed for continuing medical education credit. Some state and county programs, also supported by ATSDR, offer funding and assistance to health departments for developing educational materials and activities in environmental medicine for health care professionals.

Other opportunities for obtaining continuing education and clinical treatment information include those that are available through the American College of Occupational and Environmental Medicine, which offers a continuing education course entitled "Core Curriculum in Environmental Medicine," and the Association of Occupational and Environmental Clinics, which is a national network of clinical facilities with expertise in environmental and occupational medicine.

Details on these and many other programs offering assistance, opportunities, and information in environmental medicine are presented in Appendix D, and we urge consultation with them.

CONCLUSIONS AND RECOMMENDATIONS

There is considerable agreement that the traditions of medical education need to be adapted to a rapidly evolving social, political, and environmental context, and that there is also a need for more integration of basic and clinical sciences, increased mastery of biological concepts, increased attention to the social and behavioral aspects of health and disease, and greater use of ambulatory and community clinical experiences in the learning process. Although deep structural resistance to such change is inherent in the organization of medical schools, the current climate of expectation with respect to an increased emphasis on prevention in health care, a paradigm shift in the knowledge base, and the successes of the limited numbers of programs that support the integration and enhancement of environmental medicine in medical education are favorable to progress toward these goals. Insofar as the prospect of integrating environmental medicine into the medical school curriculum constitutes a response to the calls for curriculum reform, the climate offers opportunities for taking immediate action to enhance the content of environmental medicine in both medical education and practice. In addition, continued support and expansion of programs that currently support research and training are needed to ensure the progressive enhancement of competency in environmental medicine in medical education and practice. This should build on the success of current programs and include adequate funding to support reasonable growth and progress in curriculum development, faculty development, and continuing education.

5

Concluding Remarks

As recently as three decades ago, the environment was not of particular concern to many Americans. Today, in some areas of the United States, it is a primary issue. Of particular concern is the recognition that some environmental agents can produce insidious adverse health effects decades after exposure occurs.

For many reasons, including the need to be able to respond appropriately to their patients' concerns about the environment, physicians and other health care providers need to be knowledgeable about the effects of the environment on individual and community health. The most important reason is to increase their ability to make a positive difference in their patients' health and in the well-being of their communities, and to prevent unnecessary adverse health outcomes related to environmental (including occupational) exposures. Another reason is to allow them to be more responsive to the concerns of patients who are increasingly knowledgeable and worried about environmental health issues. These and other reasons combine to necessitate an enhancement of the education of health professionals in environmental health and medicine.

The Institute of Medicine began to address these issues in a report released in 1988 entitled *Role of the Primary Care Physician in Occupational and Environmental Medicine* (often referred to as "The Green Book" [Institute of Medicine, 1988]). That report described the relative lack of specialists in occupational and environmental medicine and how that lack hampers the usual doctor-to-doctor mechanisms of providing both informal and formal consultative support. Based on a growing need for expertise in the emerging field of environmental medicine, the report recommended that physicians improve their ability to identify conditions caused by environmental contaminants, to obtain patient histories that include environmental risk conditions, and to make appropriate diagnoses and referrals.

"The Green Book" states that most individuals with occupational or environmental illnesses obtain their medical care from physicians who are not specialists in either occupational or environmental medicine. Primarily for this reason, the report states that "at a minimum, all primary care physicians should be able to *identify possible occupationally or environmentally induced conditions* and *make the appropriate referrals for follow-up*" (Institute of Medicine, 1988:5) The report also states that primary care physicians should know basic principles of disease related to chemical exposure; know how to take an appropriate exposure history; be sensitive to the ethical, social, and legal implications of the diagnosis of environmental disease; and be alert to opportunities to prevent or mitigate illness and exposure. Two subsequent IOM reports addressed the related topics of medical information needs (Institute of Medicine, 1990) and the physician shortage in occupational and environmental medicine (Institute of Medicine, 1991).

As follow-up to the previous IOM reports in this area, the Agency for Toxic Substances and Disease Registry requested that the IOM address issues related to enhancing the content of environmental medicine in medical education; additional support was subsequently provided by the Environmental Protection Agency and the National Institute for Occupational Safety and Health. With the understanding that all medical schools are different and that what is learned is more important than what is taught, the IOM committee responded to its charge by establishing competency-based learning objectives that it felt should apply to all graduating medical students. In order to facilitate the achievement of these objectives and to implement a strategy of enhancing the integration of environmental medicine in medical education, the committee compiled a series of case studies that should be used for teaching and learning about the fundamental and myriad effects of the environment on health. It is the sense of this committee that using these cases and others like them will help teach the basic and clinical sciences and enhance the capabilities of future physicians to practice medicine.

The committee is optimistic about the ease with which these competencies can be taught, the eagerness with which they will be learned, and the improvements that will be experienced in the practice of medicine as a result of their achievement and application.

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Appendixes

A

Taking an Exposure History

ATSDR October 1992

Case Studies in Environmental Medicine

26 Taking an Exposure History

Environmental ALERT . . .

- ☑ ***Because many environmental diseases either manifest as common medical problems or have nonspecific symptoms, an exposure history is vital for correct diagnosis.***
- ☑ ***The primary care clinician can play an important role in detecting, treating, and preventing disease due to toxic exposure by taking a thorough exposure history.***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. See page 35 for more information about continuing medical education credits and continuing education units.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry
in conjunction with
Centers for Disease Control and Prevention,
National Institute for Occupational Safety and Health

Case Study

On Tuesday afternoon, a 52-year-old man with previously diagnosed coronary artery disease controlled by nitroglycerin describes episodes of recurring headache for the past 3 weeks. Mild nausea often accompanies the headache; there is no vomiting. He describes a dull frontal ache that is not relieved by aspirin. The patient states that the headaches are sometimes severe; at other times they are a nagging annoyance. The durations range from half an hour to a full day. His visit was prompted also by a mild angina attack that he suffered this past weekend, shortly after awakening on Sunday morning. He has experienced no further cardiac symptoms since that episode.

History of previous illness indicates that the patient was diagnosed with angina pectoris 3 years ago and has been taking nitroglycerin 0.4 mg sublingually prophylactically before vigorous exercise. He also takes one aspirin every other day. He has been symptom-free for the past 2 ½ years. Sublingual nitroglycerin relieved the pain of the Sunday morning angina attack within several minutes. The patient does not smoke and rarely drinks alcohol.

He is a trim man with a slightly ruddy complexion. At present, he is afebrile, and his vital signs are blood pressure 120/85, pulse 80, respirations 20. Physical examination including HEENT, heart, lungs, and neurologic exam is normal. The results of an ECG with a rhythm strip performed in your office are unremarkable. Subsequent laboratory testing reveals normal blood lipids, cardiac enzymes, CBC, sedimentation rate, glucose, creatinine, and thyroid function.

Pretest

(a) What would you include in the patient's problem list?

(b) What would you include in the differential diagnosis?

(c) What additional information would you seek to assist in the diagnosis?

Answers are on page 33.

Introduction

The preceding case study describes a patient with angina. He has new, nonspecific symptoms of headache and nausea. Suppose this patient lived near a hazardous waste site. Would your differential diagnosis change? If the patient refinished furniture as a hobby, would you consider this important? Is there a connection between his headaches and cardiac symptoms? How would you investigate the possible correlation? Could he be exposed to chemicals in his workplace? Each of these factors could play a role in the etiology of this patient's illness; each exposure could cause disease.

The patient described in the case study–a 52-year-old male with angina–is portrayed in three different scenarios throughout this document. An exposure history form, completed by the patient in each scenario, provides clues that prompt the clinician to investigate the possibility of toxic exposure.

- ***Scenario 1: This patient is an accountant who has had the same job and residence for many years.***
- ***Scenario 2: This patient owns a commercial cleaning service and uses cleaning products at various industrial and commercial sites.***
- ***Scenario 3: This patient is a retired advertising copywriter who lives in the vicinity of an abandoned industrial complex.***

Most environmental and occupational diseases either manifest as common medical problems or have nonspecific symptoms. It is the etiology that distinguishes a disorder as an environmental illness. Unless an exposure history is pursued by the clinician, the etiologic diagnosis may be missed, treatment may be inappropriate, and exposure can continue.

Most people with illness caused or exacerbated by exposure to hazardous substances obtain their medical care from clinicians who are not specialists in either environmental or occupational medicine. Few clinicians, however, routinely elicit information about the home, workplace, or community environment as part of the demographic and social history. In a study of a primary care practice in an academic setting, only 24% of 625 charts had any mention of the patient's occupation. Only 2% of the charts had information on exposures, duration of present employment, and past occupations. In addition, clinicians caring for adolescents seldom ask about their work exposure and history during routine health care visits or when evaluating symptoms.

Although many clinicians do recognize the importance of taking a work and exposure history for evaluating certain problems, most have had little training or practice in doing so. Extensive knowledge of toxicology is not needed to diagnose environmental and occupational disease. The same criteria are employed as those used in diagnosing other medical problems–history including onset and temporal pattern of symptoms, palliative and provocative factors, physical examination, and laboratory results. If necessary, consultation with industrial hygienists or environmental testing can be used. In addition to current exposures, the clinician must consider the long-term or latent effects of past exposures to agents such as asbestos, radiation, and chemical carcinogens.

Investigating environmental and occupational illness is illustrated in this monograph. The aim is not to demonstrate all exposure possibilities but rather to illustrate the principles and the *process* of investigating this etiology. The exposure history form (pages 23-26), which can be completed by the clinician or by the patient (to save staff time), will guide the clinician through various aspects of this process. The form elicits many important points of an exposure history including job descriptions and categories associated with hazardous substances, physical and biologic agents, and temporal and activity patterns related to environmental and occupational disease. The form explores past and current exposures.

Taking an exposure history requires only a few minutes of the clinician's time and can be abbreviated, expanded, or focused according to the patient's signs and symptoms. The exposure history form is designed for quick scanning of important details and can be copied and used for a permanent database as well as for the investigation of current problems.

The diagnosis of environmental or occupational disease cannot always be made with certainty. Sound clinical judgment must be used, and common etiologies should be considered. The multifactorial nature of many conditions, particularly chronic diseases, must not be overlooked.

An exposure history should be taken on every patient. It is of particular importance if the patient's illness occurs at an atypical age or is unresponsive to treatment. The clinician must also keep in mind that many organ systems are affected by toxic exposure (Table 1). The latency period from exposure to manifestation of disease can vary–ranging from immediate to delayed (hours or days) to prolonged (decades).

With practice using the exposure history form and a network of referrals, the primary care clinician can play an important role in detecting, treating, and preventing disease resulting from toxic exposures.

Organ Systems Affected by Toxic Exposure

The respiratory system is both a target organ and a portal of entry for toxicants. Adult-onset asthma and death from asthma are increasing. More than 100 toxicants are known to cause asthma, and many more can exacerbate it.

Irritant and allergic contact dermatitis account for 90% of occupational skin disorders. Other skin disorders with exposure etiologies include pigment alterations, chloracne, urticaria, and malignant neoplasms.

Alcohol abuse is a potential confounding factor in the evaluation of patients with suspected toxic exposure. However, a history of alcohol use does not necessarily exclude an environmental or occupational etiology. Symptoms of liver disease due to toxic exposure can mimic viral hepatitis.

About 4000 new cases of renal disease of unknown etiology are diagnosed annually. Organic solvents and heavy metals are two classes of toxicants known to adversely affect renal function.

Neurotoxins can cause peripheral neuropathy, ataxia, parkinsonism, seizures, coma, and death. Many chemicals cause mild central nervous system depression that may be misdiagnosed as personality disorders or that can progress to psychoses or dementia. Sensory impairment can also be caused by exposure to toxicants (e.g., visual disturbances caused by methanol) and physical agents (e.g., hearing impairment caused by loud noise).

About 200,000 infants are born annually with some form of birth defect. The causes of most of these defects are unknown.

Table 1. Organ systems often affected by toxic exposure

Organ/System	Exposure Risks
Respiratory	asbestos,* radon,* cigarette smoke, glues
Dermatologic	dioxin,* nickel, arsenic,* mercury,* cement (chromium*), PCBs,* glues, rubber cement
Liver	carbon tetrachloride,* methylene chloride,* vinyl chloride*
Kidney	cadmium,* lead,* mercury,* chlorinated hydrocarbon solvents*
Cardiovascular	carbon monoxide, noise, tobacco smoke, physical stress, carbon disulfide, nitrates,* methylene chloride*
Reproductive	methylmercury,* carbon monoxide, lead,* ethylene oxide
Hematologic	arsenic,* benzene,* nitrates,* radiation
Neuropsychologic	tetrachloroethylene,* mercury,* arsenic,* toluene,* lead,* methanol,* noise, vinyl chloride*

*This substance is covered in *Case Studies in Environmental Medicine*, which is a series of self-instructional booklets on specific chemical hazards developed by the Agency for Toxic Substances and Disease Registry (ATSDR), Division of Health Education. A complete list of titles and information on how to obtain them is on page 38.

The cardiovascular and hematologic systems are frequent targets of toxicants. Cardiovascular changes, as well as exacerbation of preexisting cardiovascular conditions, can result from exposure to noise and to chemicals such as carbon monoxide and tobacco smoke. Benzene can cause bone marrow changes leading to aplastic anemia, acute leukemia, and chronic myelogenous leukemia.

Toxicants in the Home/Environment

The clinician should consider the following sources, which are discussed below, when eliciting information on exposures in the home and environment:

- Indoor air pollution
- Common household products
- Pesticides and lawn care products
- Lead products and waste
- Recreational hazards
- Water supply
- Soil contamination

Indoor Air Pollution

Tobacco Smoke

Environmental tobacco smoke is a mixture of more than 4700 compounds. Mainstream smoke is exhaled by the smoker, and sidestream smoke comes off the smoldering end of the cigarette and is inhaled by adjacent persons (passive smokers). Sidestream smoke contains more carcinogenic hydrocarbons and respirable particles than mainstream smoke. All smokers should be encouraged to stop smoking; if household members will not refrain from smoking, they should smoke only in well-ventilated or isolated areas.

Does anyone in the household smoke? How many packs per day?

Wood Stoves/Gas Ranges

Thirteen million wood stoves are in use in the United States, and 800,000 are sold annually. When not properly maintained and vented, wood stoves emit noxious gases including carbon monoxide, oxides of nitrogen, particulates, and hydrocarbons. Studies have shown that children living in homes heated with wood stoves have a significant increase in respiratory symptoms compared with children living in homes without wood stoves.

Does the patient have a wood stove?

Is there a smoke smell indoors?

When was the last time the chimney and stove were cleaned?

Gas ranges, which may produce nitrogen oxide, a respiratory irritant, are used for cooking in more than half of U.S. homes. In low-income areas, gas stoves may be used not only for cooking but as a supplemental source of heat. Proper ventilation and routine inspection and maintenance are necessary in residences where wood or gas stoves are used.

If the patient uses a gas range, is it in proper working order?

Does the patient use the gas range for heat?

Building Materials

Building materials, home improvement products, and textiles used in the home can pose health risks. For example, formaldehyde volatilizes

Does the patient live in a mobile home?

from particle board, insulation materials, carpet adhesives, and other household products. This is a particular problem in the confined spaces of mobile homes. Formaldehyde exposure can cause rhinitis, nausea, dry skin or dermatitis, and upper respiratory and eye irritation. It has also been reported to precipitate bronchospasm in persons who have asthma.

Was urea formaldehyde foam used for insulation?

Is cabinetry or furniture made of pressed wood?

Asbestos

Was asbestos insulation used on pipes or hot water tank?

Do walls and ceilings have sprayed-on or troweled-on material?

Is renovation work planned in any of the areas containing asbestos?

Are adults in the household exposed to asbestos on the job?

Asbestos was widely used from 1950 to the early 1970s in areas requiring sound proofing, thermal proofing, or durability (e.g., floor and ceiling coverings, heating and water pipe insulation). It was often applied as a spray-on material. Asbestos that is in good condition and not respirable is generally not a risk. However, when it becomes frayed or friable (i.e., easily crumbled), asbestos fibers can be released into the air. Exposure to these fibers has been associated with lung cancer, asbestosis, and mesothelioma. The occurrence of disease is influenced by type of asbestos mineral inhaled, concentration and dimension of the fibers, and exposure duration. In 1986, the Environmental Protection Agency (EPA) estimated that friable asbestos may be present in as many as 35,000 schools in the United States, potentially exposing 15 million schoolchildren and 1.4 million adults. Smoking cigarettes, in addition to asbestos exposure, increases the risk of cancer by an order of magnitude above smoking alone or asbestos exposure alone. Children may be at greater risk than adults because of their long life expectancy, high activity rates, high breathing rates, more time spent near the floor where fibers accumulate, and greater likelihood of contact (through curiosity or mischief). (For further information on the health hazards of asbestos exposure, consult *Case Studies in Environmental Medicine: Asbestos Toxicity*, ATSDR, June 1990.)

Radon

Has the patient's home been tested for radon?

If yes, what were the results?

Are there high levels in homes in the area?

Do children spend a significant amount of time in the basement or on the first floor of the home, where radon might tend to be in higher concentrations?

Radon, a colorless, odorless gas, is a decay product of uranium found in significant concentrations in some areas. Radon itself does no harm, but its progeny attach to airborne particulates such as cigarette smoke and can be inhaled. During subsequent decay, the progeny emit high-energy alpha particles that may injure adjacent bronchial cells, thereby causing lung cancer. Five to ten percent of single-family homes in the United States have been estimated to exceed the EPA radon recommended guideline of 4 picocuries per liter of air. EPA estimates that approximately 14,000 lung cancer deaths per year are attributable to radon. (For further information about radon exposure and its health effects, see *Case Studies in Environmental Medicine: Radon Toxicity*, ATSDR, September 1992.)

Common Household Products

Does the patient use any of the following on a regular basis: cleaners for glass, oven, floors, drains, toilets, polishes, air fresheners and disinfectants, glues, solvents, paint strippers, sealants?

A 1987 EPA study found approximately 12 common organic pollutants in concentrations 2 to 5 times higher in air inside homes than in outdoor air from use of household products. Product warning labels are often inadequate and pertain to acute exposures only. Long-term or repeated use of some household chemicals, such as chlorinated hydrocarbons, can result in cancer. Commonly used compounds that can have serious adverse effects are methylene chloride (found in paint strippers and thinners, and adhesive removers), tetrachloroethylene (used in dry cleaning of clothes), and paradichlorobenzene (found in room air fresheners, toilet bowl deodorizers, and moth crystals). (See *Case Studies in Environmental Medicine: Methylene Chloride Toxicity*, ATSDR, June 1990, and *Tetrachloroethylene Toxicity*, ATSDR, June 1990.)

Where are these chemicals stored and disposed of?

Pesticides and Lawn Care Products

Pesticides and lawn care products are potentially hazardous, especially to children. Pesticide exposure can occur through dermal contact, inhalation, or ingestion. At least 1400 active ingredients can be found in more than 34,000 available preparations of insecticides, herbicides, fungicides, and other antibiologic preparations. These agents have different mechanisms of action and toxicity. Estimated annual use of these chemicals is 2.6 billion pounds.

Despite the ban on certain pesticides in the United States, exposure can still occur through improper use, storage, and disposal. Some banned pesticides are used in foreign countries and may return to this country on imported foods. Proper use and storage of household pesticides and proper cleaning of food, especially raw fruits and vegetables, can help protect consumers.

Does the patient use pesticides on the garden and lawn?

Does the patient employ a professional lawn-care company?

Are children allowed to play in areas recently sprayed with pesticides or lawn-care products?

Does the patient use bug repellants?

Does the patient know what to do in case of accidental poisoning?

Lead Products and Waste

Lead poisoning continues to be a significant health problem in the United States. Although lead was banned from paint for home use in 1972, millions of homes, particularly those built before 1950, still contain high amounts of lead in paint that is peeling and accessible for ingestion by children. Lead exposure also occurs through drinking water, especially in homes that have lead plumbing or lead-soldered pipes. Significant exposures have occurred in children who played in lead-contaminated soil. Acidic foods, such as juices, stored in imported pottery may leach lead from ceramic glazes. Some ceramic glazes used by hobbyists also may contain lead. Air can be contaminated with this metal through use of leaded gasoline. Parents can inadvertantly bring it home on their clothing and shoes, or in their cars if they work in jobs where they are exposed to lead dusts or lead-containing compounds.

More than a million U.S. workers are potentially exposed to lead daily in hundreds of occupations such as construction work, radiator repair, metals recycling, battery manufacturing, smelting, and pigments formulating. Good workplace and personal hygiene practices can prevent the majority of these "take-home" exposures.

The 1985 intervention level of 25 mg/dL has been revised downward to 10 mg/dL. Childhood lead exposure has been associated with lower class ranking and higher absenteeism in school, poor eye-hand coordination, slow reaction time, and lower vocabulary test scores. Consequences of childhood lead exposure have been shown to endure into adulthood. (See *Case Studies in Environmental Medicine: Lead Toxicity*, ATSDR, Revised September 1992.)

What year was the patient's home built? Is indoor paint in poor repair?

Is the inside of the patient's home being renovated?

Has the patient's drinking water been tested for lead?

Does the patient use imported earthenware pottery?

Do any household members work with lead (e.g., in a lead refinery or smelter, battery factory, or power plant)? If *yes*, are work clothes brought home?

Do any household members work with arts and crafts products containing lead?

Does the patient live near a lead refinery or smelter, battery factory, or power plant?

Recreational Hazards

Do the patient's children play on wooden playground equipment that has been treated and sealed?

Do the children play in a sandbox that may contain tremolite (asbestos)?

Recreational areas and products can pose a hazard to health. Fishing and swimming in contaminated lakes and streams can expose participants to toxins contained in polluted waters. Wooden playground structures that have not been treated with protective sealants may allow children to have dermal contact with potentially hazardous wood preservatives; these include arsenic-containing compounds, pentachlorophenol, and creosote. Some play sands and clays have been reported to contain asbestos-like fibers. Other materials used in arts and crafts involve potentially hazardous silica, talc, solvents, and heavy metals such as lead and cadmium. Toxic materials may be encountered in making stained glass and jewelry, woodworking, model building, and oil and airbrush painting. One need not be directly involved in these activities to become exposed; merely being in the vicinity of a work area may cause exposure. Federal legislation (Labeling of Hazardous Materials Act) will require that all chronically hazardous materials be labeled as inappropriate for children's use. (See ATSDR series *Case Studies in Environmental Medicine: Arsenic Toxicity*, June 1990; *Pentachlorophenol Toxicity*, December 1992; *Cadmium Toxicity*, June 1990; and *Asbestos Toxicity*, June 1990.)

Water Supply

What is the source of the patient's water supply?

If the patient uses a private well, when was the last time the water was tested?

Both public water supplies and private wells can be a source of toxic exposure, especially for industrial solvents, heavy metals, pesticides, and fertilizers. For example, an EPA groundwater survey detected trichloroethylene in approximately 10% of the wells tested. It is estimated to be in 34% of the nation's drinking water supplies. Up to 25% of the water supplies have detectable levels of tetrachloroethylene. Methylene chloride may remain in groundwater for years. Some solvents can volatilize from showers and during laundering of clothes, thereby creating risk of toxicity via inhalation. Nitrates, a common contaminant of rural shallow wells, pose a risk of methemoglobinemia, especially to infants. *(See* ATSDR series *Case Studies in Environmental Medicine: Asbestos Toxicity*, June 1990; *Arsenic Toxicity*, June 1990; *Lead Toxicity*, Revised September 1992; *Nitrates/Nitrites Toxicity*, October 1991; *Trichloroethylene Toxicity*, January 1992; *Methylene Chloride Toxicity*, June 1990; *Tetrachloroethylene Toxicity*, June 1990.)

Soil Contamination

Did the patient or previous owners use chlordane or other pesticides or termiticides in the home?

What is the history of the site on which the home was built?

Ingestion of contaminated soil poses a risk of toxicity, especially to children under the age of six because of natural mouthing behaviors. Lead is a common soil contaminant. Dioxin also adsorbs to soils. Certain pesticides such as chlordane can remain in the soil for years. (See ATSDR series *Case Studies in Environmental Medicine: Arsenic Toxicity*, June 1990; *Lead Toxicity*, Revised September 1992; *Dioxin Toxicity*, June 1990; *Chlordane Toxicity*, December 1992; *Cadmium Toxicity*, June 1990; *Chromium Toxicity*, June 1990.)

Using the Exposure History Form

A work and exposure history has three components: *Exposure Survey, Work History*, and *Environmental History*. The main aspects of an exposure history (summarized in Table 2) will be elicited through the exposure history form (pages 23-26). Although a positive response to any question on the form indicates the need for further inquiry, a negative response to all questions does not necessarily rule out a toxic exposure etiology or significant previous exposure.

All patients should complete exposure history forms, although the form need not be evaluated extensively in every clinical situation. As in all data-gathering activities, sound clinical judgment must be exercised.

Table 2. Components of an exposure history

Part 1. Exposure Survey
  A. Exposures
    Current and past exposure to metals, dust, fibers, fumes, chemicals, biologic hazards, radiation, noise, vibration
    Typical work day (job tasks, location, materials, agents used)
    Changes in routines or processes
    Other employees or household members similarly affected

  B. Health and Safety Practices at Worksite
    Ventilation
    Medical and industrial hygiene surveillance
    Employment exams
    Personal protective equipment (e.g., respirators, gloves, coveralls)
    Lockout devices, alarms, training, drills
    Personal habits (Smoke, eat in work area? Wash hands with solvents?)

Part 2. Work History
    Description of all prior jobs including short-term, seasonal, part-time employment and military service
    Description of present job(s)

Part 3. Environmental History
    Present and prior home locations
    Jobs of household members
    Home insulating, heating and cooling system
    Home cleaning agents
    Pesticide exposure
    Water supply
    Recent renovation/remodelling
    Air pollution, indoor and outdoor
    Hobbies: painting, sculpting, welding, woodworking, piloting, autos, firearms, stained glass, ceramics, gardening
    Hazardous wastes/spills exposure

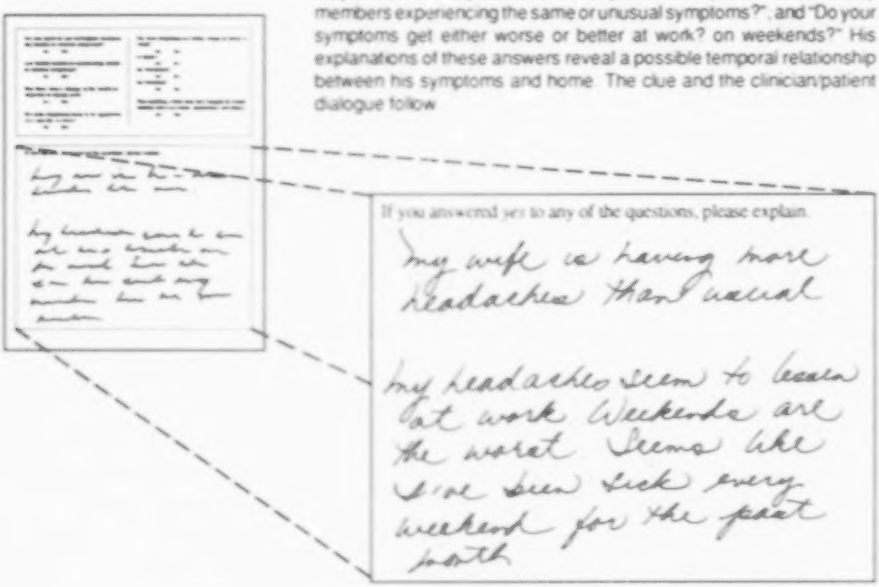
Part 1. Exposure Survey

Past and current exposures are recorded on pages 1 and 2 of the exposure history form, which is designed for easy completion by the patient and quick scanning for pertinent details by the clinician. The questions investigate the following: known exposure to metals, dust, fibers, fumes, chemicals, physical agents, and biologic hazards; details about known toxicant exposure; other persons affected; temporal patterns and activities, changes in routines and worksite characteristics, and protective equipment use.

If the patient answers *yes* to one or more questions on Part 1, the clinician must follow up by asking the patient progressively more detailed questions about the possible exposure. Special attention should be directed to the route, dose, duration, and frequency of any identified exposure.

Scenario 1 below illustrates the use of part 1 of the form with the patient described in the case study (page 1). The patient's chart reveals that he has worked as an accountant in the same office for the past 12 years. On the completed form, he indicates that no other workers are experiencing similar or unusual symptoms, and he denies recent changes in his job routine. The patient answered *yes* to three questions: "Are family members experiencing the same or unusual symptoms?", and "Do your symptoms get either worse or better at work? on weekends?" His explanations of these answers reveal a possible temporal relationship between his symptoms and home. The clue and the clinician/patient dialogue follow.

Scenario 1:
53-year-old male accountant with angina
Chief complaint: headache and nausea



If you answered yes to any of the questions, please explain.

my wife is having more headaches than usual

my headaches seem to lessen at work Weekends are the worst Seems like I've been sick every weekend for the past month

Clinician: I see that you noted that your wife is having headaches.
Patient: Yes. She has frequent headaches. In the last 3 or 4 weeks she has had more than usual. She usually has one every month or so; this past month she had three.

Clinician: You also state that your headaches are worse on weekends.
Patient: Yes, they seem to be. If I wake up on a Saturday or Sunday with a headache, it usually gets worse as the day progresses. In fact, that's usually when I feel nauseated too.

Clinician: Do your symptoms seem to be aggravated by certain activities around the home? A hobby or task?
Patient: No, I usually wake up with the headache. I don't think there's a connection with anything I do.

Clinician: Do your symptoms change at all at work?
Patient: Now that you mention it, if I wake up with a headache, by the time I get to work–it takes about 25 minutes–the headache is usually gone.

Clinician: Your angina attack occurred on a Sunday morning. Describe your weekend leading up to the attack.

Patient: It was a fairly quiet weekend. We had dinner at home Friday evening and just relaxed. On Saturday I spent the day packing old books and storing them in the attic and chopping and stacking firewood. I took one nitroglycerin tablet before doing the heavy work, at about 2 PM. Saturday night we had friends over for dinner. We had a fire in the fireplace and visited until about 11 PM. I had one glass of wine with dinner. I was beginning to feel a little stiff and sore from the work I did that afternoon. Sunday morning I woke up with a headache again. A few minutes after awakening, while I was still in bed, I had the attack. It was mild, not the crushing pain I've had in the past. I had the headache all day.

The preceding dialogue reveals that the patient's symptoms may be associated with the home environment and his cardiac symptoms, headache, and nausea may be related. His symptoms seem to be exacerbated at home and lessen at work. Further questioning is needed to pursue this lead.

Clinician: What does your wife do for a living?
Patient: She's an attorney.

Clinician: Do either one of you have a hobby?
Patient: My hobby is photography. My wife is an avid gardener.

Clinician: Do you have your own darkroom?
Patient: No, I occasionally use a friend's. For the past year I've had my film and prints processed commercially.

Clinician: Does your wife use any pesticides or chemicals in the garden?
Patient: No, she does strictly organic gardening and uses only natural means of pest control.

Clinician: Do you work on your car?
Patient: No.

Clinician: Have you gotten any new furniture or remodeled your home in the past few years?
Patient: No.

Clinician: What is your source of heating and cooking in the home?
Patient: We have a natural gas, forced-air heating system. We cook with gas and use the fireplace a lot in winter.

Clinician: How long have you lived in this home and how old is your furnace?
Patient: We've lived there for 23 years. The furnace was replaced about 12 years ago.

Clinician: I see that you recently insulated your home. What exactly did you do?
Patient: Yes. Last month I added extra insulation to the attic, insulated the crawl space, replaced all the windows with double-paned windows, and weatherized all doorways.

Clinician: Have you noticed that the headaches coincide with days you have used the fireplace?
Patient: There could be a connection. I definitely use the fireplace more on weekends. This past Saturday I had a fire blazing all day.

A temporal relationship between the headaches and being in the home has been revealed. Some sources of toxicants have been eliminated (formaldehyde and other volatile organic chemicals from new furniture and rugs; toxic chemicals used in hobbies or gardening). A correlation may exist between symptoms and use of the fireplace. The fireplace could increase negative pressure in the house, causing backdrafting of furnace gases. The furnace is old; it may be malfunctioning or producing excessive carbon monoxide. The patient's symptoms, including his angina attack, would be consistent with carbon monoxide poisoning.

Although the patient's symptoms could be associated with his preexisting disease, evidence is strong enough at this point to investigate the possibility of environmental exposure. Contacting the local gas company to request that they check the furnace and stove for malfunctions and leaks would be appropriate. The fireplace should be checked for proper drafting and for deposits of creosote in the chimney.

A carboxyhemoglobin (COHb) level on the patient may confirm carbon monoxide poisoning. The patient should be advised to ventilate the house until the furnace is checked or to stay out of the house until the gas company deems it safe. Symptoms of headaches usually do not occur below 15% COHb, but the half-life of COHb is only several hours.

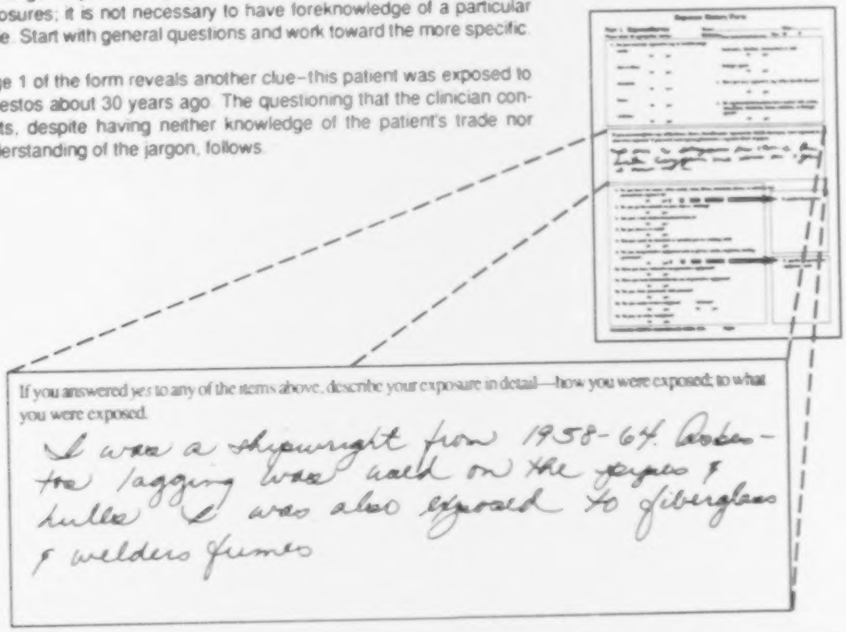
A COHb level performed on this patient is reported to be 6%, which is high for a nonsmoker. The gas company discovers a cracked heating element in the 12-year-old furnace, which resulted in carbon monoxide fumes circulating throughout the house. The use of the fireplace most likely increased the backdrafting of fumes. The furnace is replaced, the exposure ceases, and the patient's symptoms abate. He experiences no further cardiac symptoms.

It is not necessary to understand the jargon of a particular trade; persistent questioning by the clinician can clarify the tasks involved and reveal possible exposures.

The exposure history form may also alert the clinician to past exposures. Most often, neither the job title nor the patient's initial description of job duties reveals clues of exposure. It is usually helpful to have a patient describe a routine work day, as well as unusual or overtime tasks. Patients tend to use jargon when describing their jobs. It is the clinician's challenge to persistently question the patient to elucidate possible exposures; it is not necessary to have foreknowledge of a particular trade. Start with general questions and work toward the more specific.

Page 1 of the form reveals another clue–this patient was exposed to asbestos about 30 years ago. The questioning that the clinician conducts, despite having neither knowledge of the patient's trade nor understanding of the jargon, follows.

Scenario 1:
52-year-old male accountant with angina
Chief complaint: headache and nausea



If you answered yes to any of the items above, describe your exposure in detail—how you were exposed; to what you were exposed.

I was a shipwright from 1958-64. Asbestos lagging was used on the pipes & hulls. I was also exposed to fiberglass & welders fumes

Clinician: You state here that you were exposed to asbestos, fiberglass, and welders' fumes way back in '58.
Patient: Yes, during my days as a shipwright.

Clinician: Did you actually handle the asbestos?
Patient: No, the pipe laggers were the tradesmen that handled the asbestos. Oh, you might be setting a bracket or plate next to a pipe and accidentally hit the pipe and dislodge some asbestos, but otherwise, shipwrights didn't handle it. You only had asbestos where there were steamlines from the boiler carrying high-pressure steam to other units like a winch or an auxiliary motor.

Clinician: What does a shipwright do? What was a routine day for you?
Patient: There was no routine day. The shipwrights were the cream of the journeymen crop; we did everything from outfitting, to establishing the cribbing on the launching gang, to shoring. I worked on the outfitting docks. We did ship reconversions. I did a lot of work on the forepeak and hawse pipes when I wasn't working below decks.

Clinician: What exactly were your tasks below decks?
Patient: Most transporters were converted to passenger ships after the war; there was a lot of shifting of equipment and pipes. Basically, the ships were gutted. They would be completely revamped. The shipwrights would do all the woodworking, finish work, plates, and so on. Then, when everything was in place, it would be insulated and the pipes would be lagged.

Clinician: So you worked throughout the ship? And when you finished your tasks the laggers would come in?
Patient: No, no. There might be ten different tradesmen working in an afterpeak at one time. You'd be working next to welders, flangers, pipefitters, riveters, laggers; you name it. These conversions were done round-the-clock, 7 days a week; it could take a year and a half to complete a conversion. All the tasks were being done simultaneously.

Clinician: How long would the lagging take?
Patient: The lagging could take 6 to 10 months; sometimes longer. They were constantly cutting these sections of asbestos to fit the pipes. Then they would attach the sections with a paste and wrap it with asbestos wrapping.

Clinician: Could you see the asbestos in the air?
Patient: Oh yes. Sometimes it was so thick you couldn't see 5 feet in front of you. It was white and hung in the welders' fumes like smog.

Clinician: Did you use any protective equipment? Masks, respirators?
Patient: No. Nobody ever said it was dangerous. We were bothered more by the fiberglass and welders' fumes than anything. We thought

fiberglass was more dangerous because it was itchy and caused a rash. The air was blue from the welding fumes; if you worked in that for a year, you knew it was affecting you. It inspired me to go back to school and get my accounting degree. But we were blue-collar workers; we were more concerned with welders' flash, a boom breaking, or someone getting crushed between plates than we were with asbestos.

Clinician: You worked as a shipwright for 6 years?

Patient: Yes, about that. Five of those years as an outfitter on conversions.

The dialogue in which the clinician engaged the patient neither determines whether the patient's asbestos exposure was significant, nor does it confirm that he suffered adverse effects from the exposure. It is merely a starting point for investigation. The questioning establishes that approximately 30 years ago this patient received a possibly severe exposure to asbestos fibers for a duration of 5 or 6 years. Because quantitative data on this patient's exposure is impossible to obtain, a qualitative description ("Sometimes it was so thick you couldn't see 5 feet in front of you") can facilitate assessment of the exposure when consulting with an occupational medical specialist (see Appendix). In this scenario, the disclosure should prompt the clinician to monitor the patient closely for early detection of treatable health effects from asbestos exposure. A chest X ray would be advised and pulmonary function tests should be considered. Vaccination for influenza may be warranted, depending on the results of the chest X rays. Consulting an occupational medical specialist could help determine the best way to evaluate and treat this patient.

An exposure history may suggest the need for periodic monitoring by alerting the clinician to a past exposure.

In this scenario, the clinician has successfully diagnosed an illness due to an environmental toxic exposure (carbon monoxide) and has noted a significant past exposure (asbestos), which needs follow-up. Had the clinician failed to pursue an exposure history, the patient's current illness might have been misdiagnosed, treatment might have been inappropriate, or measures might not have been implemented to prevent further carbon monoxide exposure leading to a risk of continued progression of the angina, as well as coma and death involving other household occupants.

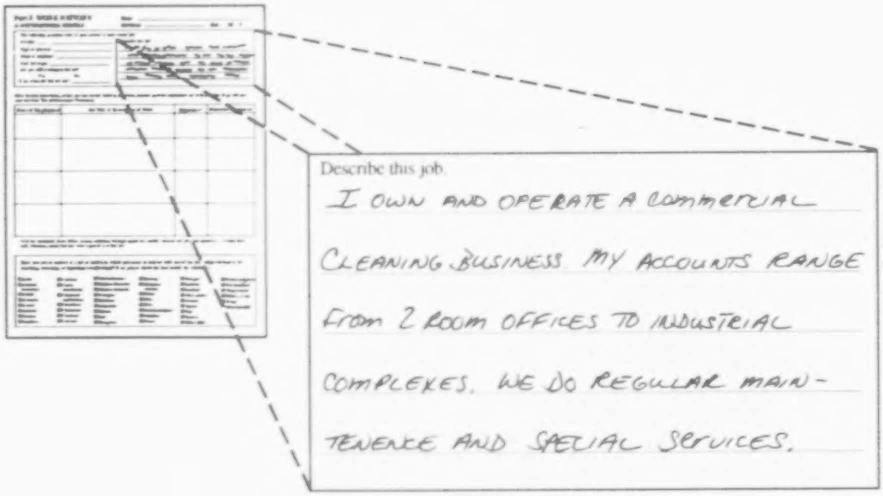
Part 2. Work History

Part 2 of the exposure history is a comprehensive inventory of the patient's occupations, employers, and current and potential exposures in the workplace. No questions on allergies and principal symptoms have been included on the presumption that the clinician will provide more detail elsewhere in the medical record.

In evaluating Part 2 of the form, the clinician should note every job the patient had, regardless of duration. Information on part-time and temporary jobs could provide clues to toxic exposure. Details of jobs may reveal exposures unexpected from the job titles. Asking if any processes or routines have been changed recently can be helpful. Military service may have involved toxic exposure.

Scenario 2 below involves another instance of a 52-year-old male with angina as described in the case study (page 1); he suffered an angina attack and complains of recurring headaches and nausea. This patient is the owner of a commercial cleaning service. He performs some of the cleaning himself. Scanning pages 1 and 2 of the form, the clinician notes that, in his work, the patient is exposed to cleaning chemicals including detergents, ammonia, and cleansers. The patient does not notice any temporal relationship of symptoms to activity. Questioning the patient extensively about the cleaning products fails to yield any suspicious exposure possibilities. Perusal of *Part 2. Work History*, however, reveals another clue. The clinician's investigation follows.

Scenario 2:
52-year-old male owner of a commercial cleaning service
Chief complaint: headache and nausea



Describe this job.

I OWN AND OPERATE A COMMERCIAL CLEANING BUSINESS. MY ACCOUNTS RANGE FROM 2 ROOM OFFICES TO INDUSTRIAL COMPLEKES. WE DO REGULAR MAIN-TENENCE AND SPECIAL SERVICES.

Clinician: You own a commercial cleaning service?
Patient: Yes, I've been in business for 10 years.

Clinician: Do you do the cleaning yourself?
Patient: I don't do as much as I used to. I have a crew of about six full-time employees. I do more managing than cleaning but I have been known to roll up my sleeves and pitch in when need be.

Clinician: You clean residences and commercial businesses?
Patient: Yes, I have 20 residential accounts and 15 commercial accounts.

Clinician: What are the commercial accounts?
Patient: The downtown administrative offices of the school district, several realty offices downtown, and the business offices of the viscose rayon mill. I have six accounts in the Shaw Building downtown–small medical offices–and five retail stores in the Hilltop Mall.

Clinician: So your headaches have been occurring for about 3 weeks now? Have there been any changes in your routine–work or otherwise–in the last 3 weeks?
Patient: I've worked more hours than usual. I've been doing a special project for the rayon mill. They built new offices. We moved all the old offices into the new building. That has entailed cleaning and moving furniture, files, books, and exhibits. It's been tedious. Fortunately, most of the staff has been either out on vacation or at an international conference in Europe; so the building has been empty. We've been able to set our own pace and come and go any day or time that suits us, so long as we clear it with security.

Clinician: Are any other workers having similar symptoms?
Patient: No, nobody else has complained about feeling sick.

Clinician: What exactly do they produce at that plant?
Patient: They make viscose–transparent paper. I used to work there during summers when I was in college. It was hot, hard work. And the whole place smelled like sulfur–rotten eggs. We used wood pulp cellulose, treated it with acids and other chemicals, and made cellulose filaments. I worked on the blending, ripening, and deaeration process.

Clinician: Can you smell the chemicals in the office building you're working in?
Patient: Some days there's a faint odor. Nothing like when I worked on the xanthating process. The business office building is on the northeast end of the complex. It's pretty remote from the processing plant.

Clinician: So how many extra hours have you worked the past 3 weeks?
Patient: Only about 10 hours each week. This past weekend I put in an extra 7 hours. I had to finish setting up the exhibits. I didn't trust the crew to handle the fragile exhibits, so I did the job myself.

Clinician: And on Sunday morning you had the angina attack. Tell me about your weekend leading up to the attack.
Patient: On Friday, I worked late setting up a huge model of the xanthating process. It was tedious work and I was sort of stressed by the time constraints to get the job done. I had broken a bottle from the exhibit when I disassembled the thing weeks ago. I was working especially carefully this time. On Saturday morning, I ran back to the plant to tie up all the loose ends and finish. In the afternoon, my wife and I spent several hours walking on the beach, despite an awful headache I had. We went to bed fairly early, about 10 PM. On Sunday morning, I had the attack. But the nitro helped almost immediately, and I had no other problems. It was pretty mild.

Clinician: What was in this bottle you broke?
Patient: I'm not sure, really. The bottle said carbon disulfide but the chemical did not smell like the carbon disulfide we used in the mill when I worked there. This stuff had a sweet odor. It was quite strong but it didn't have the nauseating rotten-egg smell of the plant.

Clinician: How did you clean it up?
Patient: I just soaked it up with rags and threw them out. The carpet dried fairly quickly.

Clinician: Did you get any of the chemical on you?
Patient: When the bottle fell and shattered, it soaked my pant leg and the toes of my shoes. I probably got some on my hands, too, when I cleaned it up.

Clinician: How much of the chemical was in the bottle? Did you report the accident to anyone at the plant?
Patient: The bottle was about a liter in size. It was full. No, I didn't report the accident. Frankly, I'm embarrassed about it. I thought I would just talk with the manager when he returns from Europe later this week.

Clinician: What did you do with the bottle?
Patient: I put the broken pieces in a paper bag and tossed it into my truck.

Clinician: Can you get it so we can read the label?
Patient: Sure. I'll call you as soon as possible.

The preceding conversation reveals a possible connection with the spill and this patient's symptoms. It warrants further investigation. The results of the patient's physical examination are normal.

The patient retrieves the broken bottle. The label on the bottle identifies the chemical–carbon disulfide–and the manufacturer. After obtaining permission from the patient, the clinician calls the manufacturer for information on carbon disulfide.

Clinician: My patient is a contract employee at a local textile company. In the process of his work he broke a bottle that was labeled carbon disulfide. He didn't report the accident and just cleaned it up himself. I am concerned that he may be experiencing health effects from the exposure.
Manufacturer: It would not surprise me. Carbon disulfide is dangerous stuff. Strict industrial controls are in effect to prevent exposure.

Clinician: He says the chemical did not smell like the carbon disulfide he remembered working with in the plant years ago. He says it had a sweet odor.
Manufacturer: The odor of the commercial grade used in the plant is altogether different from pure carbon disulfide, which I suspect was what was in the bottle he broke. Pure-grade carbon disulfide has a sweet odor.

Clinician: Can you send me information on carbon disulfide?
Manufacturer: Certainly. I'll send you a Material Safety Data Sheet on carbon disulfide today. I suggest that you report the accident to the safety manager at the textile plant.

The clinician receives a Material Safety Data Sheet on carbon disulfide (pages 29-30), reads the Health Hazard Data section, and discovers that this chemical can exacerbate cardiovascular disorders in persons receiving long-term exposure. Nausea and headache are among the acute effects of exposure, and primary routes of entry are inhalation and skin contact/absorption. Consultation with a toxicologist confirms that this patient's symptoms could indeed be caused by exposure to carbon disulfide. The clinician orders a CBC, ECG, urinalysis, tests of liver and kidney function, and determinations of COHb and electrolyte levels on this patient.

Air sampling in the office in which the incident occurred reveals airborne concentrations of 0.8 parts of carbon disulfide per million parts of air (0.8 ppm). The permissible exposure limit for an 8-hour time-weighted average is 4 ppm. The concentrations were most likely higher at the time of the incident 3 weeks ago. This indicates that besides the acute exposure the patient incurred at the time of the accident, he has been chronically exposed to carbon disulfide for the previous 3 weeks, although for a limited number of hours each week while driving with the contaminated rags and bottle in his truck.

Results of the laboratory tests on this patient, including the COHb level, all are within normal limits. The patient's exposure ceases, and he experiences no further symptoms. The clinician continues to monitor the patient's angina, which remains stable. Other employees at risk of exposure from this spill are also examined; none incurred acute exposure or suffered ill effects. At the suggestion of the clinician, the safety manager at the mill instructs the employees in proper safety practices and no further incidents occur.

Part 3. Environmental History

Part 3 of the exposure history form contains questions regarding the home and surrounding environment of the patient. Dialogue with the patient should include queries about the location of the house, water supply, and changes in air quality.

Proximity to industrial complexes and hazardous waste sites could cause residents' exposure to toxicants in the air, water, or soil. Community contamination is a growing public health concern; affected persons usually seek care first from their primary care providers. If a group of people with similar symptoms and exposures is identified, and an environmental exposure problem is suspected, the clinician should call the state health department or the federal Agency for Toxic Substances and Disease Registry at (404) 639-0615. (See Referral Resources, page 31, and the Appendix for more information.)

Are chemicals used in a well-ventilated place?

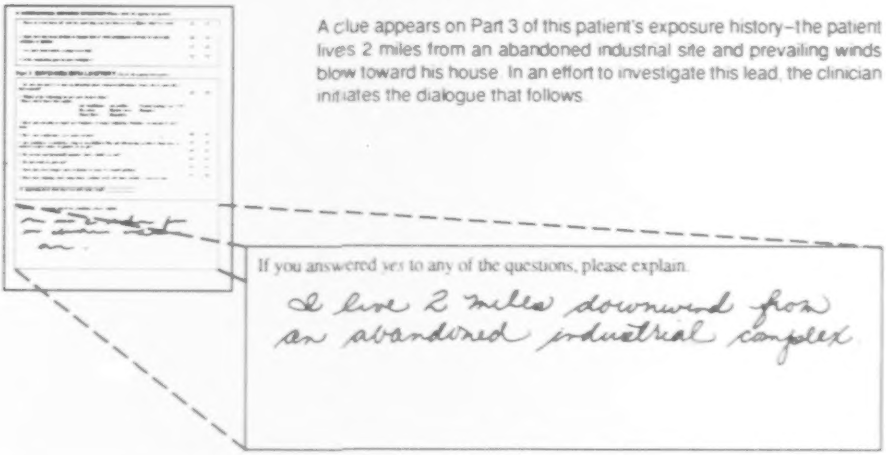
Is protective equipment used?

Hobbies are potential sources of toxicant exposure. For instance, model building, pottery-making, silk screening, gardening, stained-glass making, and woodworking all have been associated with hazardous exposure. Ask the patient what his or her hobbies are. All members in a household may be exposed to the hazardous substances from one person's hobby; small children may be especially susceptible.

Scenario 3:
52-year-old male, retired advertising copywriter with angina
Chief complaint: headache and nausea

Scenario 3 involves another patient described in the case study (page 1). In this scenario, the patient has been retired for 2 years; he took early retirement from a stressful job in advertising shortly after being diagnosed with angina. The patient's answers to the questions on the Exposure Survey (part 1 of the form) were *no*: he denies exposure to metals, chemicals, fibers, dust, radiation, and physical and biologic agents; he is not aware of a connection between his symptoms and activity or time; and to his knowledge other persons are not experiencing similar symptoms.

A clue appears on Part 3 of this patient's exposure history–the patient lives 2 miles from an abandoned industrial site and prevailing winds blow toward his house. In an effort to investigate this lead, the clinician initiates the dialogue that follows.



If you answered yes to any of the questions, please explain.

I live 2 miles downwind from an abandoned industrial complex

Clinician: You state that you live several miles downwind from an abandoned industrial site. Do you know what chemicals might have been used at the site or what type of industry it was?
Patient: There was a fire at the site several weeks ago. The newspaper said that they used methylene chloride to make some kind of plastics. The firefighters found drums of methylene chloride buried on the property.

Clinician: Do you ever smell chemicals in the air?
Patient: Yes, in the mornings when the wind blows from that direction, I sometimes smell a sweet odor. My neighbors have mentioned it too. In fact, they told me that the smell is really strong when they do laundry or dishes, and when they shower.

Clinician: Have you smelled it in your water?
Patient: No.

Clinician: What is the source of your water?
Patient: I have city water, but my neighbors have a private well.

Clinician: Do you know if any agency is testing your neighborhood for contamination?
Patient: Not as far as I know.

The preceding dialogue has uncovered a possibility that the patient was exposed to a toxicant. Furthermore, this patient may represent an index case; others may also be exposed. To follow up this lead, the clinician contacts the state health department. The health department confirms that the site contains buried drums of methylene chloride and that it is under investigation.

An industrial hygienist employed by the health department informs the clinician that the methylene chloride can indeed exacerbate signs and symptoms of angina. The odor threshold for the chemical is 100 to 300 parts per million (ppm). An 8-hour exposure to 250 ppm methylene chloride can cause a COHb level above 8%.

The laboratory reports that the patient's COHb is 6%, indicating probable exposure to methylene chloride in this nonsmoker. The clinician calls the 24-hour consultation number ([404] 639-0615) of the Agency for Toxic Substances and Disease Registry (ATSDR), Emergency Response and Consultation Branch, for more information. The clinician is advised that COHb, which forms when methylene chloride metabolizes to carbon monoxide, can be detected in blood at levels of 4% to 9% when ambient air concentrations of methylene chloride are about 200 ppm. Many factors can influence body burden, including exposure level and duration, route of exposure, physical activity, and amount of body fat. A conference call with the emergency response coordinator, a toxicologist, an industrial hygienist, and a physician to discuss the patient's signs and symptoms ensues. The clinician is given the local Association of Occupational and Environmental Clinics (AOEC) contact, who recommends a specialist who will provide follow-up care for this patient.

Results of the health department's tests of ambient air reveal no immediate crisis in the vicinity, although the levels are high; test results of water samples from private wells in the area are pending. ATSDR informs the regional office of the EPA of the situation. EPA provides immediate assistance to the affected area, clean-up is initiated, and threats to the surrounding population are mitigated.

Exposure History Form

Part 1. Exposure Survey

Please circle the appropriate answer

Name: ______________________ **Date:** __________

Birthdate: ________________ **Sex:** **M** **F**

1. Are you currently exposed to any of the following?

metals
no *yes*

dust or fibers
no *yes*

chemicals
no *yes*

fumes
no *yes*

radiation
no *yes*

loud noise, vibration, extreme heat or cold
no *yes*

biologic agents
no *yes*

2. Have you been exposed to any of the above *in the past?*
no *yes*

3. Do any household members have contact with metals, dust, fibers, chemicals, fumes, radiation, or biologic agents?
no *yes*

If you answered *yes* to any of the items above, describe your exposure in detail—how you were exposed; to what you were exposed. If you need more space, please use a separate sheet of paper.

4. Do you know the names of the metals, dusts, fibers, chemicals, fumes, or radiation that you are/were exposed to?
no *yes*

If *yes*, list them below.

5. Do you get the material on your skin or clothing?
no *yes*

6. Are your work clothes laundered at home?
no *yes*

7. Do you shower at work?
no *yes*

8. Can you smell the chemical or material you are working with?
no *yes*

9. Do you use protective equipment such as gloves, masks, respirator, hearing protectors?
no *yes*

If *yes*, list the protective equipment used.

10. Have you been advised to use protective equipment?
no *yes*

11. Have you been instructed in the use of protective equipment?
no *yes*

12. Do you wash your hands with solvents?
no *yes*

13. Do you smoke at the workplace? At home?
no *yes* *no* *yes*

14. Do you eat at the workplace?
no *yes*

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15. Do you know of any coworkers experiencing similar or unusual symptoms?
no *yes*

16. Are family members experiencing similar or unusual symptoms?
no *yes*

17. Has there been a change in the health or behavior of family pets?
no *yes*

18. Do your symptoms seem to be aggravated by a specific activity?
no *yes*

19. Do your symptoms get either worse or better at work?
no *yes*

at home?
no *yes*

on weekends?
no *yes*

on vacation?
no *yes*

20. Has anything about your job changed in recent months (such as duties, procedures, overtime)?
no *yes*

If you answered *yes* to any of the questions, please explain.

Page 2

Part 2. Work History

A. Occupational Profile

Name: ______________________________

Birthdate: ____________________ **Sex:** M F

The following questions refer to your current or most recent job:

Job title: ____________________

Type of industry: ____________________

Name of employer: ____________________

Date job began: ____________________

Are you still working in this job?

Yes No

If no, when did this job end? ____________________

Describe this job:

____

____

____

____

____

Fill in the table below listing all jobs you have worked including short-term, seasonal, part-time employment, and military service. Begin with your most recent job. Use additional paper if necessary.

Dates of Employment	Job Title and Description of Work	Exposures*	Protective Equipment

*List the chemicals, dusts, fibers, fumes, radiation, biologic agents (i.e., molds, viruses) and physical agents (i.e., extreme heat, cold, vibration, noise) that you were exposed to at this job.

Have you ever worked at a job or hobby in which you came in contact with any of the following by breathing, touching, or ingesting (swallowing)? If yes, please check the box beside the name.

☐ Acids
☐ Alcohols (industrial)
☐ Alkalies
☐ Ammonia
☐ Arsenic
☐ Asbestos
☐ Benzene
☐ Beryllium
☐ Cadmium
☐ Carbon tetrachloride
☐ Chlorinated naphthalenes
☐ Chloroform
☐ Chloroprene
☐ Chromates
☐ Coal dust
☐ Dichlorobenzene
☐ Ethylene dibromide
☐ Ethylene dichloride
☐ Fiberglass
☐ Halothane
☐ Isocyanates
☐ Ketones
☐ Lead
☐ Manganese
☐ Mercury
☐ Methylene chloride
☐ Nickel
☐ PBBs
☐ PCBs
☐ Perchloroethylene
☐ Pesticides
☐ Phenol
☐ Phosgene
☐ Radiation
☐ Rock dust
☐ Silica powder
☐ Solvents
☐ Styrene
☐ Talc
☐ Toluene
☐ TDI or MDI
☐ Trichloroethylene
☐ Trinitrotoluene
☐ Vinyl chloride
☐ Welding fumes
☐ X rays
☐ Other (specify)

Developed by ATSDR in cooperation with NIOSH, 1992 Page 3

B. Occupational Exposure Inventory *Please circle the appropriate answer.*

1. Have you ever been off work for more than one day because of an illness related to work?	*no*	*yes*
2. Have you ever been advised to change jobs or work assignments because of any health problems or injuries?	*no*	*yes*
3. Has your work routine changed recently?	*no*	*yes*
4. Is there poor ventilation in your workplace?	*no*	*yes*

Part 3. Environmental History *Please circle the appropriate answer.*

1. Do you live next to or near an industrial plant, commercial business, dump site, or nonresidential property?	*no*	*yes*

2. Which of the following do you have in your home?
Please circle those that apply.

Air conditioner	Air purifier	Central heating (gas or oil?)
Gas stove	Electric stove	Fireplace
Wood stove	Humidifier	

3. Have you recently acquired new furniture or carpet, refinished furniture, or remodeled your home?	*no*	*yes*
4. Have you weatherized your home recently?	*no*	*yes*
5. Are pesticides or herbicides (bug or weed killers; flea and tick sprays, collars, powders, or shampoos) used in your home or garden, or on pets?	*no*	*yes*
6. Do you (or any household member) have a hobby or craft?	*no*	*yes*
7. Do you work on your car?	*no*	*yes*
8. Have you ever changed your residence because of a health problem?	*no*	*yes*

9. Does your drinking water come from a private well, city water supply, or grocery store?

____

10. Approximately what year was your home built?______________

If you answered *yes* to any of the questions, please explain.

Identifying Hazardous Agents

Identifying the toxicant, stopping the exposure, and arresting or reversing the progression of the patient's illness are the goals of the exposure history. Often, patients do not know the chemicals to which they have been exposed although they may know the trade names or slang terms for the chemicals. Likewise, household products used by patients may have labeling that is inadequate for proper identification. A variety of printed reference sources are available to the clinician, including books, journals, and Material Safety Data Sheets (MSDSs). Other sources of information are described in the Appendix.

Material Safety Data Sheet

The Occupational Safety and Health Administration (OSHA) has developed a right-to-know regulation covering three basic areas: the generation and distribution of information about chemical hazards, requirements for the labeling of chemicals used in the workplace, and programs for training employees in the safe use of these chemicals. Many state and local right-to-know laws, however, are more comprehensive than the federal regulation.

The Material Safety Data Sheet (MSDS) is a component of the right-to-know law. Manufacturers and importers are required to provide an MSDS for each hazardous chemical in a shipment. Users of the chemicals must keep copies of MSDSs and make them available to workers, clinicians, or others. MSDSs contain information on the chemical properties of the substance, handling precautions, known health effects, and conditions that might worsen with exposure. The information on human health effects, however, can be vague and may have limited clinical value. The MSDS may not provide information on the synergistic effects of multiple chemical exposures. Clinical decisions should not be made solely from information obtained from MSDSs. (See MSDS, pages 29-30.)

Additional Toxicologic Information

Books and journals provide the most accessible information on toxicologic issues. Some sources of information that the clinician can use to identify the chemicals, processes, and hazards of toxic substances are described below.

> Hathaway G, Proctor NH, Hughes JP, Fischman, M, eds. Proctor and Hughes, Chemical hazards of the workplace. 3rd ed. New York: Van Nostrand Reinhold, 1991. *A short text summarizing the most important occupational chemical hazards.*
>
> Sullivan JB Jr, Krieger GR, eds. Hazardous materials toxicology: clinical principles of environmental health. Baltimore: Williams & Wilkins, 1991. *A complete reference including epidemiology, principles of management and evaluation of*

toxic exposures, toxic hazards of specific industries and sites, and economic implications of medical and legal issues.

Gosselin RE, Smith RP, Hodge HC, eds. Clinical toxicology of commercial products. Baltimore: Williams & Wilkins, 1984. *A classification of products and the chemicals they contain, including the adverse health effects produced by exposure.*

Fay BA, Billings CE, eds. Index of signs and symptoms of industrial diseases. Atlanta: U.S. Dept. of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, 1981. *A guide to occupational and environmental diseases listed by associated clinical signs and symptoms.*

Daugaard J. Symptoms and signs in occupational disease: a practical guide. Chicago: Year Book Medical Publishers, 1978. *A classification of occupational and environmental diseases according to associated clinical signs and symptoms.*

Rosenstock L, Cullen BR, eds. Clinical occupational medicine. Philadelphia: WB Saunders, 1986. *Complete coverage of the clinical aspects of occupational medicine.*

LaDou J. Occupational medicine. Norwalk, Connecticut: Appleton & Lange, 1990. *Aids in the diagnosis, treatment, and remedial measures of occupational injuries and illnesses.*

Last J, Wallace RB, eds. Maxcy-Rosenau-Last public health and preventive medicine. 13th ed. Norwalk, Connecticut: Appleton & Lange, 1992. *Although communicable diseases continue to be the main focus of this book, increased emphasis has been placed on environmental and behavioral factors that can influence health.*

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Material Safety Data Sheets Collection:

Sheet No. 350
Carbon Disulfide

Issued 11/77 Revision: D, 3/92

Section 1. Material Identification

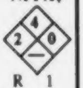
Carbon Disulfide (CS$_2$) Description: Prepared industrially by heating charcoal with vaporized sulfur or by reaction of natural petroleum fractions with sulfur. Used in manufacturing soil disinfectants, electronic vacuum tubes, viscose rayon, cellophane, flotation agents, ammonium salts and carbon tetrachloride; in insecticides, chemical analysis, electroplating, fumigation, oil extraction, dry cleaning and degreasing; and as a solvent for lipids, sulfur, rubber, oils, resin and waxes.
Other Designations: CAS No. 75-15-0, carbon bisulfide, dithiocarbonic anhydride, sulphocarbonic anhydride, Weeviltox.
Manufacturer: Contact your supplier or distributor. Consult latest *Chemical Week Buyers' Guide*(73) for a suppliers list.

Cautions: Carbon disulfide is a highly flammable, dangerous explosion hazard. It is irritating to eyes, skin, and mucous membranes, and toxic to the central nervous (CNS), peripheral nervous (PNS), and cardiovascular (CVS) systems.

‡ The NFPA health rating of "2" is misleading due to the severity of this material's toxicity to the CNS, CVS, and PNS and its chronic effects. A "3" is more appropriate.

HMIS
H 3*
F 4
R 0
PPG†
* Sec. 6, Chronic Effects
† Sec. 8

NFPA‡



R 1
I 4
S 3§
K 4
§Skin absorption

Section 2. Ingredients and Occupational Exposure Limits

Carbon disulfide, ca 99% (major impurities are sulfur compounds)

1990 OSHA PELs (Skin)
8-hr TWA: 4 ppm (12 mg/m^3)
15-min STEL: 12 ppm (36 mg/m^3)

1990 NIOSH RELs
TWA: 1 ppm (10 mg/m^3)
STEL: 10 ppm (30 mg/m^3)

1990 IDLH Level
500 ppm

1991-92 ACGIH TLV (Skin)
TWA: 10 ppm (31 mg/m^3)

1990 DFG (Germany) MAKs
TWA: 10 ppm (30 mg/m^3)
Peak Exposure Limit: 20 ppm/30 min /4 x/shift, momentary value
Half-life: <2 hr

1985-86 Toxicity Data*
Human, inhalation, TC$_{Lo}$: 40 mg/m^3/91 weeks produced paternal effects (spermatogenesis)
Human, inhalation, LC$_{Lo}$: 2000 ppm/5 min; no toxic effects noted
Human, oral, LD$_{Lo}$: 14 mg/kg; toxic effects not yet reviewed
Rat, oral, LD$_{50}$: 3188 mg/kg

* See NIOSH, *RTECS* (FF6650000), for additional mutation, reproductive and toxicity data.

Section 3. Physical Data

Boiling Point: 115 °F (46.5 °C)
Freezing Point: -168 °F (-110.8 °C)
Vapor Pressure: 300 mm Hg at 68 °F (20 °C)
Vapor Density (air = 1): 2.64
Coefficient of Viscosity: 0.363 at 68 °F (20 °C)

Molecular Weight: 76.13
Specific Gravity: 1.2632 at 68 °F (20 °C)
Water Solubility: Slightly, 220 mg/100 cc water at 71.6 °F (22 °C)
Other Solubilities: Soluble in alcohol, benzene and ether
Refraction Index: 1.66232 at 77 °F (25 °C)

Appearance and Odor: Clear, colorless to slightly yellow liquid with a sweet, chloroform-like odor when pure and a foul, rotten egg smell as the commercial product. The odor threshold is 0.1 to 0.2 ppm.
Comments: From both health effect and fire/explosion perspectives, this liquid's very high vapor pressure at room temperature indicates that airborne concentrations can build quickly to dangerous levels. Take precautions to ensure safety (Sec. 8).

Section 4. Fire and Explosion Data

Flash Point: -22 °F (-30 °C), CC
Autoignition Temperature: 194 °F (90 °C)
LEL: 1.5% v/v
UEL: 50% v/v

Extinguishing Media: Foams are more effective in carbon disulfide fires than previously believed, when water and dry chemical were the preferred extinguishing agents. Four foams tested are listed in order of increasing effectiveness: high-expansion, aqueous film-forming, fluoroprotein, and protein. If foam is unavailable, rely on carbon dioxide (CO$_2$) or water spray. Do not scatter material with more water than necessary to put out fire.
Unusual Fire or Explosion Hazards: Carbon disulfide's burning rate is 2.7 mm/min. Vapor may travel to an ignition source and flash back. Container may explode in heat of fire. CS$_2$ poses a vapor explosion hazard indoors, outdoors, and in sewers. Carbon disulfide can be ignited by friction, rusted or hot steam pipes, and may accumulate static electricity. Heat from an ordinary light bulb is enough to cause ignition.
Special Fire-fighting Procedures: Since fire may produce toxic thermal decomposition products, wear a self-contained breathing apparatus (SCBA) with a full facepiece operated in pressure-demand or positive-pressure mode. Structural firefighters' protective clothing is ineffective for fires involving carbon disulfide. Apply cooling water to sides of tanks until long after fire is extinguished. Stay away from ends of tanks. Immediately withdraw from area if you hear a rising sound from venting safety device or notice any tank discoloration due to fire. Be aware of runoff from fire control methods. Do not release to sewers or waterways.

Section 5. Reactivity Data

Stability/Polymerization: Carbon disulfide is stable at room temperature in closed containers under normal storage and handling conditions. Hazardous polymerization cannot occur.
Chemical Incompatibilities: Carbon disulfide will decompose to its elements in contact with mercury fulminate. It is incompatible with alkali metals, chlorine and other halogens, nitrogen oxide, metal azides, oxidants, aluminum, ethylene diamine and zinc. Carbon disulfide reacts exothermically with phenyl copper-triphenylphosphine complexes.
Conditions to Avoid: Exposure to ignition sources and contact with incompatibles.
Hazardous Products of Decomposition: Thermal oxidative decomposition of carbon disulfide can produce carbon monoxide (CO), carbon dioxide (CO$_2$), and toxic sulfur oxides (SO$_x$)

Section 6. Health Hazard Data

Carcinogenicity: The IARC,(164) NTP,(142) and OSHA(164) do not list carbon disulfide as a carcinogen. **Summary of Risks:** CS$_2$ enters the body primarily via the lungs (inhalation) but can be absorbed via skin. It is irritating to skin, eyes, and mucous membranes and can cause serious damage to CVS, CNS, and PNS. CS$_2$ is cardiotoxic (toxic to heart), thrombotoxic (adversely affecting blood-clotting ability), and arrythmagenic (causing irregular heartbeat). A Parkinsonian-like effect is sometimesobserved. Exposure to 60 to 100 ppm for a short time can result in severe intoxication and death. Exposure to 5000 ppm is rapidly fatal. 70 to 90% of CS$_2$ is metabolized, with lungs and kidney excreting the rest. **Medical Conditions Aggravated by Long-Term Exposure:** Coronary heart disease and CNS disorders. **Target Organs:** Skin, CNS, PNS, CVS, eyes, liver, kidney.

Continue on next page

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No. 350 Carbon Disulfide 3/92

Section 6. Health Hazard Data, *continued*

Primary Entry Routes: Inhalation and skin contact/absorption. **Acute Effects:** CS_2 is irritating and corrosive to the eyes, skin, and mucous membranes. Introduction into eyes causes burning pain, red and swelling lids, and conjunctivitis. Skin contact with liquid may lead to burning and second- or third-degree burns. CS_2 defats tissue and skin sensitization may occur. Skin absorption can result in peripheral nerve damage. Other symptoms from inhalation or skin absorption include headache, dizziness, euphoria, convulsions, nausea, vomiting, muscle weakness, and in severe cases may lead to death by respiratory failure. **Chronic Effects:** Chronic exposure to carbon disulfide may increase the risk of arteriosclerosis as well as cause delirium, psychosis, bad dreams leading to insomnia, CNS damage, peripheral neuropathies (abnormal and usually degenerative state of the nerves causing pain and unstimulated sensations), appetite loss, tremors, gastric disturbances, liver dysfunction, optical neuritis, and retinal hemorrhages. In women, chronic exposure to carbon disulfide can cause menstrual disorders. Spontaneous abortions and premature births are reported.

FIRST AID

Eyes: Gently lift eyelids and flush immediately and continuously with flooding amounts of water until transported to an emergency medical facility. *Do not* allow victim to rub or keep eyes tightly shut. Consult a physician immediately. **Skin:** *Quickly* remove contaminated clothing. Rinse with flooding amounts of water for at least 15 min. Wash exposed area with soap and water. For reddened or blistered skin, consult a physician. **Inhalation:** Remove exposed person to fresh air and support breathing as needed. **Ingestion:** Never give anything by mouth to an unconscious or convulsing person. Contact a poison control center. Unless the poison control center advises otherwise, have that *conscious and alert* person drink 1 to 2 glasses of water, then induce vomiting with 1 to 2 tablespoons of Ipecac (adult dose). After patient vomits, give 2 tablespoons activated charcoal in 8 oz. of water to drink.

After first aid, get appropriate in-plant, paramedic, or community medical support.

Note to Physicians: Since effects may be delayed, keep victim under observation. The iodine-azide test is useful in detecting degree of exposure and hypersusceptibility of exposed workers. I.V. urea 0.5 to 1.5 g/kg is recommended to inactivate free carbon disulfide in the blood. Vitamin B6 in large doses is recommended. Obtain CBC, EKG, urinalysis, and electrolyte balance.

Section 7. Spill, Leak, and Disposal Procedures

Spill/Leak: *Plan and design appropriate emergency-response procedures prior to carbon disulfide spills or leaks.* Immediately notify safety personnel, isolate area, deny entry and stay upwind. Shut off all ignition sources. Cleanup personnel should wear fully encapsulating, vapor-protective clothing to protect against contamination. If possible, detoxify material before cleanup. For small spills, take up with earth, sand, vermiculite or other absorbent, noncombustible material and place in clean, dry containers with a secure lid for later disposal. For large spills, flush liquid to a special retention basin where it can collect under a layer of water (to prevent ignition or explosion) for disposal or reclamation. Perform all cleanup operations with nonsparking tools. Follow applicable OSHA regulations (29 CFR 1910.120). **Environmental Transport:** If released to water, carbon disulfide should volatilize with a half-life of 2.6 hr (according to model river plan) and should not bioconcentrate significantly in aquatic organisms. In the atmosphere, CS_2 reacts with atomic oxygen and photochemically produced hydroxyl radicals with a half-life of 9 days. **Environmental Toxicity Values:** Sunfish, LC_{100}, 100 µg/L/hr; trout, LC_{100}, 500 µg/L/0.1 hr. **Soil Absorption/Mobility:** Carbon disulfide is highly mobile and volatilizes or leaches into soil. **Disposal:** Large amounts of CS_2 may be distilled for reclamation and packaged for reuse. Contact your supplier or a licensed contractor for detailed recommendations. Follow applicable Federal, state, and local regulations.

EPA Designations

Listed as a RCRA Hazardous Waste (40 CFR 261.33): No. P022
Listed as a CERCLA Hazardous Substance* (40 CFR 302.4): Reportable Quantity (RQ), 100 lb (45.4 kg) [* per RCRA, Sec. 3001 and CWA 311(b)(4)]
Listed as a SARA Extremely Hazardous Substance (40 CFR 355)
Listed as a SARA Toxic Chemical (40 CFR 372.65)

OSHA Designations

Listed as an Air Contaminant (29 CFR 1910.1000, Table Z-1-A)

Section 8. Special Protection Data

Goggles: Wear protective eyeglasses or chemical safety goggles, per OSHA eye- and face-protection regulations (29 CFR 1910.133). Because contact lens use in industry is controversial, establish your own policy. **Respirator:** Seek professional advice prior to respirator selection and use. Follow OSHA respirator regulations (29 CFR 1910.134) and, if necessary, wear a MSHA/NIOSH-approved respirator. Select respirator based on its suitability to provide adequate worker protection for given working conditions, level of airborne contamination, and presence of sufficient oxygen. For 10 ppm, use any chemical cartridge respirator with organic vapor cartridges. For 50 ppm, air-purifying respirator with organic vapor cartridges and a full facepiece. For emergency or nonroutine operations (cleaning spills, reactor vessels, or storage tanks), wear an SCBA. *Warning! Air-purifying respirators do not protect workers in oxygen-deficient atmospheres.* If respirators are used, OSHA requires a respiratory protection program that includes at least: training, fit-testing, periodic environmental monitoring, maintenance, inspection, cleaning, and convenient, sanitary storage areas. **Other:** Wear chemically protective gloves, boots, aprons, and gauntlets to prevent all skin contact. Suggested materials for protective clothing include polyvinyl alcohol (PVA) and polyethylene with breakthrough times of 8 and 4 hr, respectively. **Ventilation:** Provide general and local explosion-proof exhaust ventilation systems to maintain airborne concentrations below the OSHA PEL (Sec. 2). Local explosion-proof exhaust ventilation is preferred because it prevents contaminant dispersion into the work area by controlling it at its source.(103) **Safety Stations:** Make available in the work area emergency eyewash stations, safety/quick-drench showers, and washing facilities. **Contaminated Equipment:** Separate contaminated work clothes from street clothes. Launder contaminated work clothing before wearing. Remove this material from your shoes and clean personal protective equipment. **Comments:** Never eat, drink, or smoke in work areas. Practice good personal hygiene after using this material, especially before eating, drinking, smoking, using the toilet, or applying cosmetics.

Section 9. Special Precautions and Comments

Storage Requirements: Protect containers from physical damage. Store in iron, glass, porcelain or steel containers. Keep small quantities in cool, dry, well-ventilated area away from incompatibles (Sec. 5). Store large quantities in tanks; add water or inert gas (such as nitrogen) to fill emptying tanks. Submerge tanks in water or locate them above concrete basins large enough to hold the tanks' contents. Equip storage facilities with automatic sprinklers and test regularly. Outside or detached storage is preferred.

Engineering Controls: To reduce potential health hazards, use sufficient dilution or local exhaust ventilation to control airborne contaminants and to maintain concentrations at the lowest practical level. To prevent static sparks, electrically ground all system parts including piping, valves, and moveable containers. Prohibit electrical installations and heating facilities in or near storage areas. Never transfer carbon disulfide by means of air pressure; use pump, water, or inert gas. Use wooden sticks (no spark potential) to measure the contents of CS_2 tanks and containers.

Administrative Controls: Consider preplacement and periodic medical exams of exposed workers that emphasize eyes, skin, CNS, PNS, CVS, and reproductive system, and perform electrocardiograms.

Transportation Data (49 CFR 172.101, .102)

DOT Shipping Name: Carbon bisulfide or Carbon disulfide
DOT Hazard Class: Flammable liquid
ID No.: UN1131
DOT Label: Flammable liquid
DOT Packaging Exceptions: None
DOT Packaging Requirements: 173.121

IMO Shipping Name: Carbon disulphide
IMO Hazard Class: 3.1
ID No.: UN1131
IMO Label: Flammable liquid, Poison
IMDG Packaging Group: I

***MSDS Collection* References:** 26, 38, 73, 89, 100, 101, 103, 124, 126, 127, 132, 136, 140, 149, 153, 159, 162, 163, 164

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Summary and Follow-up

In each scenario, the clinician's pursuit of the exposure history led to discovery of toxic exposure for each of the three patients. In each case, the diagnosis and treatment might have been inappropriate without an exposure history. The process required only a few minutes of the clinician's time; each history was focused as indicated by the patient's reported symptoms. Using the exposure history in managing the patients' problems, as well as guiding the patients in appropriate preventive behaviors, is the practice of preventive medicine at its best.

Consultation

Industrial hygienists, who are often employed by state health departments or industry, are a source of information to the clinician investigating a possible toxic exposure. Industrial hygiene is the discipline devoted to the recognition, evaluation, and control of workplace-related factors or stresses that may cause illness, impaired health or well-being, or significant discomfort and inefficiency among workers or community members. Other medical specialists, such as clinicians specializing in occupational/environmental and general preventive medicine, can be helpful in assessing whether a significant exposure has occurred. Occupational health nurses, who often work at patients' worksites, also have expertise and experience that may be valuable to the clinician.

Referral Resources

The clinician is encouraged to build a network of occupational and environmental medical specialists for information, consultation, and referral. The Association of Occupational and Environmental Clinics (AOEC) is a network of clinics that provide professional training, community education, exposure and risk assessment, clinical evaluations, and consultative services. Educational Resource Centers (ERCs) have been established in academic centers by the National Institute for Occupational Safety and Health (NIOSH) to educate professionals in occupational medicine topics. ERCs offer training courses in occupational and environmental medicine topics; continuing medical education credit is available. Other resources, including poison control centers and government agencies, are listed and described in the Appendix, pages 39-56.

Suggested Reading List

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Levy BS, Wegman DH, eds. Occupational health: recognizing and preventing work-related disease. 2nd ed. Boston: Little, Brown & Company, 1988.

Mayer JL, Balk SJ. A pediatrician's guide to environmental toxins. Contemporary Pediatrics 1988; Part 1:5(7):22-40; Part 2: 5(8):63-76.

National Research Council. Environmental tobacco smoke: measuring exposure and assessing health effects. Washington, DC: National Academy Press, 1986.

Rogan WJ. The sources and routes of childhood chemical exposures. J Pediatr 1980;97:861.

Rom WN, ed. Environmental and occupational medicine. 2nd ed. Boston: Little, Brown & Company, 1992.

The Western Journal of Medicine. December 1982. *Entire issue devoted to occupational and environmental medicine.*

Zenz C, ed. Developments in occupational medicine. Chicago: Mosby Year Book Medical Publishers, 1980.

Zenz C, ed. Occupational medicine: principles and practical applications. 2nd ed. Chicago: Mosby Year Book Medical Publishers, 1988. *Third edition due for release in April 1993.*

Sources of Information

More information on taking an exposure history can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Taking an Exposure History* is one of a series. For other publications in this series, please use the order form on page 38. For clinical inquiries, contact ATSDR, Division of Health Education, Office of the Director, at (404) 639-6204.

Answers to Pretest

Pretest questions are on page 1.

(a) The patient's problem list includes recurrent headache and nausea, and unstable angina pectoris.

(b) The patient's differential diagnosis of chest pain includes myocardial infarction. The differential diagnosis of headache and nausea includes viral syndrome, tension headaches, migraine, brain tumor, tooth or sinus problems, psychogenic headache, medication reaction (nitroglycerin can cause headaches), and exposure to toxicants.

(c) The additional information sought to make a diagnosis would include all aspects of a work and exposure history.

B

Medical School Courses and Clerkships: Access Points for Integrating Environmental Medicine

A specific course in environmental medicine may be useful but is not necessary to achieve the competency-based learning objectives described in this report. These objectives can be achieved by integrating an enhancement of environmental medicine into existing disciplines, courses, and clerkships or clinical rotations. In an effort to illustrate this integrative approach, this appendix provides brief examples of how courses and clerkships/clinical rotations can be used as access points for introducing or emphasizing the environmental medicine competencies outlined in the report. These courses and clerkships/clinical rotations (e.g., pharmacology, pathology, pulmonology, hematology, pediatrics, obstetrics/gynecology) are common to all medical curricula regardless of how the curricula are constructed and delivered (e.g., whether they are problem-based or traditional).

The courses are presented first, followed by clerkships/clinical rotations, and both are presented alphabetically as follows, with their page numbers.

COURSES

Biochemistry and Physiology, 99
Community Medicine/Public Health, 99
Epidemiology and Biostatistics, 100
Genetics, 101
Introduction to Clinical Medicine, 101
Microbiology, 103
Neuroscience, 103
Nutrition, 104
Pathology, 105
Pharmacology, 105

CLERKSHIPS/CLINICAL ROTATIONS

Cardiovascular Medicine, 106
Dermatology, 107
Emergency Medicine, 108
Endocrinology, 109
Family Medicine, 109
Gastrointestinal Disease, 110
Hematology/Oncology, 111
Infectious Disease, 111
Internal Medicine, 112
Nephrology, 113
Neurology, 113
Obstetrics and Gynecology, 114
Orthopedics, 115
Otolaryngology, 115
Pediatrics, 116
Pulmonary Medicine, 117
Psychiatry, 118
Radiology, 118

For each of the courses and clerkships presented below, we briefly discuss the relationship of environmental factors to the discipline and list relevant case studies from Appendix C that can be used for teaching and learning purposes (Index 2 of Appendix C lists specific case studies according to courses and clerkships). These lists are not meant to be all-inclusive, and creative teachers and students may find additional applications. Using these case studies should help to impart knowledge about environmental medicine along with that of the individual, specific discipline. [Note: Indexes in Appendix C facilitate the use of the case studies by presenting them according to (1) agent and condition, (2) courses and clerkships, (3) sentinel pathophysiological conditions for environmental and occupational evaluation, and (4) clinical signs, symptoms, and presenting complaints.]

MEDICAL SCHOOL COURSES

Instruction in the basic sciences during the first year in medical school includes diverse courses encompassing a variety of the biological sciences. Several of these disciplines include the basic sciences that form the backbone of environmental medicine. Among these are biochemistry, genetics, pharmacology, pathology, and neuroscience. This appendix contains examples for use in teaching aspects of environmental medicine within many of these courses, with the intention of demonstrating that this curriculum content can and should become an integral component of these courses. This integration of examples of environmental medicine into core courses in the preclinical years may also facilitate more effective teaching of the sciences, since applied examples often motivate students, stimulate discussion, and enhance overall comprehension of the discipline.

Biochemistry and Physiology

Courses in biochemistry and physiology could include examples drawn from environmental medicine. In these courses, the use of examples of exposure-induced perturbations of normal function often will serve to inject medical relevance, motivating students in their approach to the subject. When the examples are directly relevant to the material at hand, they reinforce the material and stress its importance.

Selected Case Studies From Appendix C

Case No.	Title
7	Fetal Death Due to Nonlethal Maternal Carbon Monoxide Poisoning
12	Cyanide Toxicity
18	Lead Poisoning from Mobilization of Bone Stores During Thyrotoxicosis
19	Lead Toxicity
24	Methylene Chloride Toxicity
25	Paint-Remover Hazard
26	Fatal Outcome of Methemoglobinemia in an Infant
27	Nitrate/Nitrite Toxicity
29	Pentachlorophenol Toxicity
35	Polynuclear Aromatic Hydrocarbon (PAH) Toxicity
36	Polychlorinated Biphenyl (PCB) Toxicity

Community Medicine/Public Health

Courses in community medicine and public health introduce students to the major causes of morbidity and mortality, the distribution of disease in populations, community and population-based approaches for protecting and promoting public health, and the organization and delivery of services and programs to address broad public health problems. Given that the environment has always occupied a prominent place in the public health model of disease, these courses provide an ideal venue for teaching and learning about the impact of environmental factors on health and disease. For example, these courses provide opportunities for students to learn about the impact of pollution and hazardous waste on human health; environmental and occupational hazards affecting particular populations (e.g., children, medical students in their own "work" environment); community-based resources for addressing occupational and environmental health risks, questions, and concerns; and methods for preventing and controlling environmentally-related illness and injury.

Selected Case Studies From Appendix C

Case No.	Title
17	Hantavirus Pulmonary Syndrome: A Clinical Description of 17 Patients with a Newly Recognized Disease
20	Legionnaires' Disease: Description of an Epidemic of Pneumonia
30	Aldicarb Poisoning: A Case Report with Prolonged Cholinesterase Inhibition and Improvement After Pralidoxime Therapy
31	Cholinesterase-Inhibiting Pesticide Toxicity
32	Infertility in Male Pesticide Workers
33	Pesticide Food Poisoning from Contaminated Watermelons in California, 1985
34	Poisoning of an Urban Family Due to Misapplication of Household Organophosphate and Carbamate Pesticides
38	Radon Toxicity
39	Residential Radon Exposure and Lung Cancer in Sweden
40	Community Outbreaks of Asthma Associated with Inhalation of Soybean Dust
54	Childhood Asthma and Indoor Environmental Risk Factors
55	Populations at Risk From Particulate Air Pollution—United States, 1992

Epidemiology and Biostatistics

Epidemiology and biostatistics are the core disciplines necessary for clinicians to develop an understanding of environmental disease. These courses contain the central scientific framework that distinguishes the population-based approach of environmental and occupational medicine and other public health disciplines from much of clinical medicine. Especially important for environmental and occupational medicine are the approaches used to measure or estimate exposure to potential harmful agents. For students, epidemic outbreaks provide an exciting venue for learning both the basic science of epidemiology and biostatistics and for raising their awareness of the importance of public health. This is an excellent context for introducing statistical concepts (e.g., power of the test), measures of risk (e.g., odds ratios, relative risk, and attributable risk), and sources of bias (e.g., selection, measurement, confounding, and the healthy worker effect). Among the compelling outbreaks are asthma epidemics related to unloading of grain in the ports of New Orleans and Barcelona and carbamate pesticide poisoning due to contaminated watermelons in California. Finally, these courses provide an appropriate setting for addressing the translation of population studies into individual risk estimation for patients.

Selected Case Studies From Appendix C

Case No.	Title
17	Hantavirus Pulmonary Syndrome: A Clinical Description of 17 Patients with a Newly Recognized Disease
20	Legionnaires' Disease: Description of an Epidemic of Pneumonia
31	Cholinesterase-Inhibiting Pesticide Toxicity
32	Infertility in Male Pesticide Workers
33	Pesticide Food Poisoning from Contaminated Watermelons in California, 1985
38	Radon Toxicity
39	Residential Radon Exposure and Lung Cancer in Sweden
40	Community Outbreaks of Asthma Associated with Inhalation of Soybean Dust
54	Childhood Asthma and Indoor Environmental Risk Factors
55	Populations at Risk From Particulate Air Pollution—United States, 1992

Genetics

Although there has been extensive interest in the relationship between environmental and hereditary factors in genetics, this relationship has not been sufficiently clarified to recommend its use in existing courses. While the literature does now include many putative examples of gene-environment interactions pertinent to medicine, they remain speculative enough that their inclusion in a course should be elective, perhaps complementing discussions of the Human Genome initiative and its medical relevance for practicing physicians.

Selected Case Studies From Appendix C

Case No.	Title
29	Pentachlorophenol Toxicity
37	Ionizing Radiation
38	Radon Toxicity

Introduction to Clinical Medicine

The introduction to clinical medicine (ICM) course is commonly taught in the first years of medical school and may run across semesters. Although it does not necessarily provide students with their first patient contact, it remains the traditional locus for teaching the theory and especially the practice of taking a complete medical history and performing a physical exam. Typically, students are assigned to interview and examine

6 to 12 patients, write up these encounters in a fairly standard format (e.g., chief complaint; history of present illness; past medical history), and turn them in to a preceptor for discussion and critique. The write-ups are long and require that students practice all aspects of history-taking on all patients, rather than focussing only on what appears to be relevant to the patient's presenting illness. A parallel focus in this type of course usually involves many hours of pathophysiology lectures on the organ systems. The following suggestions are based on this format.

As stated in Chapter 3, history-taking is the key skill for promoting and developing the other competencies in a manner that is integrated with patient care. It is well known that house staff and physicians in private practice generally are not skilled in eliciting an occupational and environmental history from patients. This is not a difficult skill to master, but it does require practice and a sense of territorial familiarity to encourage further practice and skill building. All standard medical texts list "occupation" as part of the "social history," and some go on to list "toxic exposure" and other details as well. However, we believe that course directors and preceptors typically do not teach students to value this portion of the history, and thus they soon lose interest in it. There is little extrinsic reward for students' doing a good job on the environmental and occupational history, and little or no consequence for ignoring it. If this perception is acquired in a "leisurely" ICM setting, students will not practice this aspect of history-taking and will not have the competency in their repertoire when they confront the more demanding third-year clerkships. Thus, we propose that an emphasis be placed on environmental/occupational history-taking from the outset in the ICM course.

Students should be explicitly required to perform and write down a detailed environmental/occupational history on all patients they interview, whether or not it is relevant to the presenting illness, just as a detailed family history or sexual history is taken on all of the ICM patients. This should include the current or most recent, usual occupation, with a job description, and a list of any toxic or other exposures experienced (e.g., ergonomic hazards) and protective equipment used. All previous jobs should be listed. Students should be encouraged to ask patients to clarify any unfamiliar terms that come up during the interview. Patients' homes should be described in terms of their heating system, air conditioning, type of building materials, water supply, and presence of problems with agents such as radon; lead paint; wood, kerosene, or other smoke; unvented appliances; water-damaged carpets or structural materials; proximity to known hazardous waste sites; and pesticide use. Enforcing this requirement needs attention, because most preceptors cannot be expected to give it high priority, as they will not feel completely competent themselves. One solution is to enforce it in a parallel course that has specific responsibility for environmental and occupational issues and make this part of history-taking and the ICM write-up dovetail with its own teaching objectives. Otherwise, specific leadership from the ICM course director will be necessary, with some attention to see that practice occurs. If history-taking patterns are allowed to develop without this skill, environmental/occupational history-taking skills will be exceedingly hard to retrofit in the future. An important benefit of this component of history-taking is building rapport with patients. Discussion of a patient's work and home generally helps to improve the physician-patient relationship. Appendix A contains the ATSDR case study on "Taking an Exposure History" and provides an excellent example and source of material for teaching and learning the skill of taking good environmental and occupational histories.

Selected Case Studies

Case No.	Title
Appendix A	Taking an Exposure History

Microbiology

Courses in microbiology use clinical examples to demonstrate either pathophysiologic aspects of illness due to an organism or public health aspects such as reservoirs, vectors, and susceptibility. The listed examples, as well as others, such as TB transmission in hospitals, demonstrates the overlap between environmental investigations and microbiology, sometimes leading to recognition of new pathogens.

Selected Case Studies From Appendix C

Case No.	Title
17	Hantavirus Pulmonary Syndrome: A Clinical Description of 17 Patients with a Newly Recognized Disease
20	Legionnaires' Disease: Description of an Epidemic of Pneumonia

Neuroscience

Environmental causes of nervous system disease are surprisingly common and the environmental and occupational causes of both peripheral and central nervous system diseases are well described. The agents and exposures responsible for these conditions provide a wealth of opportunities for exploration of the biology, cellular physiology, and anatomy of the central and peripheral nervous systems.

Selected Case Studies From Appendix C

Case No.	Title
1	Arsenic Toxicity
2	Seasonal Arsenic Exposure from Burning Chromium-Copper-Arsenate-Treated Wood
8	Carbon Tetrachloride Toxicity

9	Chlordane Toxicity
18	Lead Poisoning from Mobilization of Bone Stores During Thyrotoxicosis
19	Lead Toxicity
21	Mercury in House Paint as a Cause of Acrodynia: Effect of Therapy with N-Acetyl-D, L-Penicillamine
22	Mercury Toxicity
23	Methanol Toxicity
24	Methylene Chloride Toxicity
30	Aldicarb Poisoning: A Case Report with Prolonged Cholinesterase Inhibition and Improvement After Pralidoxime Therapy
31	Cholinesterase-Inhibiting Pesticide Toxicity
33	Pesticide Food Poisoning from Contaminated Watermelons in California, 1985
34	Poisoning of an Urban Family Due to Misapplication of Household Organophosphate and Carbamate Pesticides
41	Tetrachloroethylene Toxicity
42	Toluene Toxicity
45	Trimethyltin Encephalopathy
48	Work-Related Disorders of the Neck and Upper Extremity

Nutrition

The relationship between environmental hazards and nutrition is intimate but often subtle; courses in nutrition provide an excellent setting to reach environmental health and provide a wealth of relevant examples. Most obviously, food and water provide a major source for environmental contaminants, such as occurred in Minimata Bay in Japan (organic mercurials concentrated in sea fish). Less obviously, choices of diet impact the long-term bioaccumulation of hazardous materials, such as pesticide residues and PCBs. Some environmental toxicants act by competition with micronutrients, such the role of goitragens in blocking iodine uptake and metabolism. Finally, evidence is accumulating that the biological effects of toxicants may be modified by dietary behaviors, such as recent evidence suggesting a chemopreventive effect of various antioxidants.

Selected Case Studies From Appendix C

Case No.	Title
2	Seasonal Arsenic Exposure from Burning Chromium-Copper-Arsenate-Treated Wood
6	Cadmium Toxicity
18	Lead Poisoning from Mobilization of Bone Stores During Thyrotoxicosis

33	Pesticide Food Poisoning from Contaminated Watermelons in California, 1985

Pathology

Pathologists have long realized the importance of environmental disease. The teaching of "environmental pathology" has been standard practice within this discipline for many years, and the major texts in pathology include sections on environmental disease. For a well-known minority of conditions, especially pneumoconioses, pathologic examination can provide both a tissue and an etiologic diagnosis. More commonly, specific etiologic diagnoses will require information from a patient's medical history to supplement the tissue diagnosis, as in the case of hypersensitivity pneumonitis, toxic neuropathy, hepatotoxicity, and malignancy. Nevertheless, the pathologic features of each of the above-mentioned conditions can often suggest toxic etiologies over other types of pathophysiology, and such cases provide excellent material for clinicopathologic correlation.

Selected Case Studies From Appendix C

Case No.	Title
3	Asbestos Toxicity
4	Benzene Toxicity
8	Carbon Tetrachloride Toxicity
37	Ionizing Radiation
38	Radon Toxicity

Pharmacology

The teaching of pharmacology in medical school is primarily targeted at the therapeutic use of pharmaceuticals. The clinician is primarily interested in the use of drugs to prevent and treat human disease, as well as to ameliorate suffering. Therefore, general courses in pharmacology in medical school are aimed at providing a rational basis for the clinical use of therapeutics. At the same time, it is important that the physician be concerned about exposure to chemical agents, such as through environmental pollution and industrial wastes. This is a recognized component of pharmacology but often assumes a secondary role in the education process. We suggest that the teaching of pharmacology in medical schools include, as a central part of the curriculum, examples of the pharmacology of environmental and work-related toxicants, as well as pharmaceutical therapeutics. The general principles of pharmacology are directly applicable to such disease-causing agents, and there are many examples that can be integrated into the teaching of pharmacology at almost every level. A wide variety of toxicants can serve as examples for teaching about absorption, transformation, and excretion, and the various classes of compounds.

Selected Case Studies From Appendix C

Case No.	Title
4	Benzene Toxicity
7	Fetal Death Due to Nonlethal Maternal Carbon Monoxide Poisoning
8	Carbon Tetrachloride Toxicity
12	Cyanide Toxicity
16	Gasoline Toxicity
18	Lead Poisoning from Mobilization of Bone Stores During Thyrotoxicosis
19	Lead Toxicity
26	Fatal Outcome of Methemoglobinemia in an Infant
27	Nitrate/Nitrite Toxicity
28	An Outbreak of Nitrogen Dioxide-Induced Respiratory Illness Among Ice Hockey Players
30	Aldicarb Poisoning: A Case Report with Prolonged Cholinesterase Inhibition and Improvement After Pralidoxime Therapy
31	Cholinesterase-Inhibiting Pesticide Toxicity
33	Pesticide Food Poisoning from Contaminated Watermelons in California, 1985
34	Poisoning of an Urban Family Due to Misapplication of Household Organophosphate and Carbamate Pesticides

CLERKSHIPS/CLINICAL ROTATIONS

In the clinical or clerkship years of medical school, students receive instruction in several areas, such as pediatrics, psychiatry, and general internal medicine. We discuss these areas below and a few others that are common in most medical curricula. Each area is discussed briefly in terms of the relevance of environmental factors. This is followed by a list of selected case studies from Appendix C that can be used for illustrative purposes in each of the disciplines.

Cardiovascular Medicine

The pathophysiology of the cardiovascular system includes examples of disease caused by environmental agents. Both acute and chronic heart disease have been related to environmental and occupational exposures. However, the precise mechanisms of toxicity of some of the compounds associated with heart disease are poorly understood.

Selected Case Studies From Appendix C

Case No.	Title
7	Fetal Death Due to Nonlethal Maternal Carbon Monoxide Poisoning
12	Cyanide Toxicity
19	Lead Toxicity
23	Methanol Toxicity
24	Methylene Chloride Toxicity
25	Paint-Remover Hazard
26	Fatal Outcome of Methemoglobinemia in an Infant
27	Nitrate/Nitrite Toxicity
29	Pentachlorophenol Toxicity
30	Aldicarb Poisoning: A Case Report with Prolonged Cholinesterase Inhibition and Improvement After Pralidoxime Therapy
31	Cholinesterase-Inhibiting Pesticide Toxicity
33	Pesticide Food Poisoning from Contaminated Watermelons in California, 1985
34	Poisoning of an Urban Family Due to Misapplication of Household Organophosphate and Carbamate Pesticides

Dermatology

Any abnormality or inflammation of the skin that is either directly or indirectly attributable to exposures or actions at work constitutes an occupational skin disorder. There is an enormous variety of cutaneous reactions and clinical skin disorders that are related to work and the general environment. In fact, skin disorders are among the most frequently reported environmental and occupational diseases. Patterns of exposure-induced injury can be very specific in some cases or they may present as non-specific inflammatory change. Thus, environmental and occupational causes of all types of dermatologic disorders should be considered in the teaching of the differential diagnoses of skin disease.

Selected Case Studies From Appendix C

Case No.	Title
1	Arsenic Toxicity
2	Seasonal Arsenic Exposure from Burning Chromium-Copper-Arsenate-Treated Wood
11	Chromium Toxicity
13	Dioxin Toxicity

21	Mercury in House Paint as a Cause of Acrodynia: Effect of Therapy with N-Acetyl-D, L-Penicillamine
22	Mercury Toxicity
29	Pentachlorophenol Toxicity
36	Polychlorinated Biphenyl (PCB) Toxicity
49	Contact Dermatitis in Surgeons from Methylmethacrylate Bone Cement
50	Skin Lesions and Environmental Exposures: Rash Decisions

Emergency Medicine

Emergency physicians are typically confronted with acutely ill individuals, and their primary focus must be on the stabilization of vital signs. However, people exposed to some environmental asphyxiants such as cyanide, pesticides, and carbon monoxide benefit from specific therapy and need to be correctly diagnosed at the outset. Inhalation injury to the respiratory tract requires a consideration of immediate management, such as whether to hospitalize individuals for observation of delayed pulmonary edema, as well as an appreciation of delayed consequences of exposure, such as reactive airways dysfunction syndrome (RADS). Consideration needs to be given to treatment of standard smoke inhalation as well as to agents that cause delayed pulmonary edema or bronchiolitis (phosgene, nitrogen dioxide). A consideration of RADS as a late outcome of irritant inhalation is also pertinent.

Selected Case Studies From Appendix C

Case No.	Title
2	Seasonal Arsenic Exposure from Burning Chromium-Copper-Arsenate-Treated Wood
7	Fetal Death Due to Nonlethal Maternal Carbon Monoxide Poisoning
10	Chronic Reactive Airway Disease Following Acute Chlorine Gas Exposure in an Asymptomatic Atopic Patient
12	Cyanide Toxicity
30	Aldicarb Poisoning: A Case Report with Prolonged Cholinesterase Inhibition and Improvement After Pralidoxime Therapy
31	Cholinesterase-Inhibiting Pesticide Toxicity
33	Pesticide Food Poisoning from Contaminated Watermelons in California, 1985
34	Poisoning of an Urban Family Due to Misapplication of Household Organophosphate and Carbamate Pesticide

Endocrinology

Environmental toxicants uncommonly cause major endocrine disturbances, except in the setting of overwhelming (accidental) exposures, such as to the biocide Vacor, a cause of acquired diabetes. More commonly, however, environmental factors may complicate endocrine alterations, or interact with them. A current area of exciting inquiry is the possibility that many carcinogenic agents, such as pesticides, may act via steroid receptors, such as the estrogen receptor in breast tissue.

Selected Case Studies From Appendix C

Case No.	Title
18	Lead Poisoning from Mobilization of Bone Stores During Thyrotoxicosis
32	Infertility in Male Pesticide Workers

Family Medicine

Many of the clinical concerns in the family medicine curriculum can be found in this appendix under specific disciplines such as pediatrics, internal medicine, and obstetrics. Here we suggest a focus on the household environment, including contaminants introduced by parents' work, hobbies, pets, and personal habits. Clinical problems that emphasize the shared home environment are best taught where all family members are covered by the same health care provider.

Selected Case Studies From Appendix C

Case No.	Title
1	Arsenic Toxicity
2	Seasonal Arsenic Exposure from Burning Chromium-Copper-Arsenate-Treated Wood
3	Asbestos Toxicity
4	Benzene Toxicity
5	Beryllium Toxicity
8	Carbon Tetrachloride Toxicity
11	Chromium Toxicity
13	Dioxin Toxicity
14	Ethylene/Propylene Glycol Toxicity
15	Formalin Asthma in Hospital Staff
17	Hantavirus Pulmonary Syndrome: A Clinical Description of 17 Patients with a Newly Recognized Disease
18	Lead Poisoning from Mobilization of Bone Stores During Thyrotoxicosis
19	Lead Toxicity

20	Legionnaire's Disease: Description of an Epidemic of Pneumonia
21	Mercury in House Paint as a Cause of Acrodynia: Effect of Therapy with N-Acetyl-D, L-Penicillamine
22	Mercury Toxicity
24	Methylene Chloride Toxicity
26	Fatal Outcome of Methemoglobinemia in an Infant
27	Nitrate/Nitrite Toxicity
28	An Outbreak of Nitrogen Dioxide-Induced Respiratory Illness Among Ice Hockey Players
30	Aldicarb Poisoning: A Case Report with Prolonged Cholinesterase Inhibition and Improvement After Pralidoxime Therapy
31	Cholinesterase-Inhibiting Pesticide Toxicity
32	Infertility in Male Pesticide Workers
33	Pesticide Food Poisoning from Contaminated Watermelons in California, 1985
34	Poisoning of an Urban Family Due to Misapplication of Household Organophosphate and Carbamate Pesticides
42	Toluene Toxicity
43	Occupational Asthma Due to Toluene Diisocyanate Among Velcro-Like Tape Manufacturers
48	Work-Related Disorders of the Neck and Upper Extremity
54	Childhood Asthma and Indoor Environmental Risk Factors

Gastrointestinal Disease

Exposure-induced hepatotoxins are well known. Any course on gastroenterology includes a significant amount of time devoted to the study of liver dysfunction. Many causes of liver dysfunction are presented and studied in depth. Often, such discussions are aimed at the clinical consequences of hepatic insufficiency as a result of pharmaceuticals; alternatively, the use of pharmaceuticals in patients with liver dysfunction can also be discussed. We urge that courses include a discussion of environmental sources of hepatotoxic compounds including alcohol and other hepatotoxins such as polychlorinated biphenyls (PCBs), vinyl chloride, and chromium.

Selected Case Studies From Appendix C

Case No.	Title
8	Carbon Tetrachloride Toxicity
11	Chromium Toxicity
18	Lead Poisoning from Mobilization of Bone Stores During Thyrotoxicosis
27	Nitrate/Nitrite Toxicity

30	Aldicarb Poisoning: A Case Report with Prolonged Cholinesterase Inhibition and Improvement After Pralidoxime Therapy
31	Cholinesterase-Inhibiting Pesticide Toxicity
33	Pesticide Food Poisoning from Contaminated Watermelons in California, 1985
34	Poisoning of an Urban Family Due to Misapplication of Household Organophosphate and Carbamate Pesticides
36	Polychlorinated Biphenyl (PCB) Toxicity
47	Vinyl Chloride Toxicity

Hematology/Oncology

Courses in hematology routinely include study of the biochemistry and function of the erythrocyte. As part of this, heme synthesis and the protoporphyrin pathway are addressed in detail. In addition, causes of anemia are addressed, including the forms attributable to environmental and occupational exposures. Therefore, many of these exposures can be introduced easily into the teaching of hematology and oncology.

Selected Case Studies From Appendix C

Case No.	Title
3	Asbestos Toxicity
4	Benzene Toxicity
11	Chromium Toxicity
13	Dioxin Toxicity
18	Lead Poisoning from Mobilization of Bone Stores During Thyrotoxicosis
19	Lead Toxicity
26	Fatal Outcome of Methemoglobinemia in an Infant
35	Polynuclear Aromatic Hydrocarbon (PAH) Toxicity
37	Ionizing Radiation
38	Radon Toxicity
39	Residential Radon Exposure and Lung Cancer in Sweden
46	Trichloroethylene Toxicity
47	Vinyl Chloride Toxicity

Infectious Disease

Instruction in infectious disease provides many rich examples of the application of epidemiology in medicine. Epidemic evaluation includes many cases where attention is focused upon illnesses that are environmental in the broadest sense. The principles of evaluation of clusters of infectious disease are also instructive for other applications, including disease caused by workplace exposures and other environmental agents.

Selected Case Studies From Appendix C

Case No.	Title
17	Hantavirus Pulmonary Syndrome: A Clinical Description of 17 Patients with a Newly Recognized Disease
20	Legionnaires' Disease: Description of an Epidemic of Pneumonia

Internal Medicine

An internal medicine clerkship is an excellent opportunity to refine pathophysiologic knowledge and is especially useful for developing clinical skills critical to environmental/occupational medicine. Students must develop clinical judgment about when to pursue environmental/occupational etiologies. We suggest an approach of triage, where it is recognized that some pathophysiologic entities are more likely to have underlying environmental/occupational etiologies than others. For these conditions or complaints, environmental/occupational causes should always be carefully considered and should be included in the development of a differential diagnosis and consideration of pertinent negatives during oral presentations.

Selected Case Studies From Appendix C

Case No.	Title
1	Arsenic Toxicity
2	Seasonal Arsenic Exposure from Burning Chromium-Copper-Arsenate-Treated Wood
4	Benzene Toxicity
8	Carbon Tetrachloride Toxicity
11	Chromium Toxicity
14	Ethylene/Propylene Glycol Toxicity
15	Formalin Asthma in Hospital Staff
17	Hantavirus Pulmonary Syndrome: A Clinical Description of 17 Patients with a Newly Recognized Disease
18	Lead Poisoning from Mobilization of Bone Stores During Thyrotoxicosis
20	Legionnaires' Disease: Description of an Epidemic of Pneumonia
24	Methylene Chloride Toxicity
30	Aldicarb Poisoning: A Case Report with Prolonged Cholinesterase Inhibition and Improvement After Pralidoxime Therapy
31	Cholinesterase-Inhibiting Pesticide Toxicity
32	Infertility in Male Pesticide Workers

33	Pesticide Food Poisoning from Contaminated Watermelons in California, 1985
34	Poisoning of an Urban Family Due to Misapplication of Household Organophosphate and Carbamate Pesticides
42	Toluene Toxicity
43	Occupational Asthma Due to Toluene Diisocyanate Among Velcro-Like Tape Manufacturers
48	Work-Related Disorders of the Neck and Upper Extremity

Nephrology

Kidney pathology is complex and includes many aspects of basic sciences in discussing glomerular filtration and iron transport. Specific patterns of renal injury are associated with many toxicants and pharmaceuticals.

Selected Case Studies From Appendix C

Case No.	Title
1	Arsenic Toxicity
2	Seasonal Arsenic Exposure from Burning Chromium-Copper-Arsenate-Treated Wood
6	Cadmium Toxicity
8	Carbon Tetrachloride Toxicity
14	Ethylene/Propylene Glycol Toxicity
18	Lead Poisoning from Mobilization of Bone Stores During Thyrotoxicosis
19	Lead Toxicity
21	Mercury in House Paint as a Cause of Acrodynia: Effect of Therapy with N-Acetyl-D, L-Penicillamine
22	Mercury Toxicity
23	Methanol Toxicity

Neurology

The neurologic approach, much like the internal medicine approach, focuses on the etiologic evaluation of certain complaints and pathophysiologic states.

Selected Case Studies From Appendix C

Case No.	Title
1	Arsenic Toxicity
2	Seasonal Arsenic Exposure from Burning Chromium-Copper-Arsenate-

	Treated Wood
8	Carbon Tetrachloride Toxicity
9	Chlordane Toxicity
18	Lead Poisoning from Mobilization of Bone Stores During Thyrotoxicosis
19	Lead Toxicity
21	Mercury in House Paint as a Cause of Acrodynia: Effect of Therapy with N-Acetyl-D, L-Penicillamine
22	Mercury Toxicity
23	Methanol Toxicity
24	Methylene Chloride Toxicity
30	Aldicarb Poisoning: A Case Report with Prolonged Cholinesterase Inhibition and Improvement After Pralidoxime Therapy
31	Cholinesterase-Inhibiting Pesticide Toxicity
33	Pesticide Food Poisoning from Contaminated Watermelons in California, 1985
34	Poisoning of an Urban Family Due to Misapplication of Household Organophosphate and Carbamate Pesticides
41	Tetrachloroethylene Toxicity
42	Toluene Toxicity
45	Trimethyltin Encephalopathy
48	Work-Related Disorders of the Neck and Upper Extremity

Obstetrics and Gynecology

Most commonly students will need to respond to patient concerns about the potential implications of an environmental or occupational exposure to a pregnancy or a desired pregnancy. Counseling and data gathering are more germane than diagnosis in this context. There is a defined, and likely incomplete, list of environmental and occupational agents with reproductive and developmental effects.

Selected Case Studies From Appendix C

Case No.	Title
7	Fetal Death Due to Nonlethal Maternal Carbon Monoxide Poisoning
9	Chlordane Toxicity
18	Lead Poisoning from Mobilization of Bone Stores During Thyrotoxicosis
19	Lead Toxicity
30	Aldicarb Poisoning: A Case Report with Prolonged Cholinesterase Inhibition and Improvement After Pralidoxime Therapy
31	Cholinesterase-Inhibiting Pesticide Toxicity

33	Pesticide Food Poisoning from Contaminated Watermelons in California, 1985
34	Poisoning of an Urban Family Due to Misapplication of Household Organophosphate and Carbamate Pesticides
37	Ionizing Radiation
44	1,1,1-Trichloroethane
53	Reproductive and Developmental Hazards

Orthopedics

Any organ-systems course that discusses the physiology of musculoskeletal injury should also address rapid alternating movement as a source of morbidity. Vibration-induced disease as a cause of musculoskeletal injury is well studied and well understood. Ergonomics is a discipline that should be familiar to most physicians. Students would do well to learn the principles of ergonomics since back pain and other musculoskeletal conditions will form a significant portion of any adult primary-care practice.

Selected Case Studies From Appendix C

Case No.	Title
6	Cadmium Toxicity
48	Work-Related Disorders of the Neck and Upper Extremity

Otolaryngology

The teaching of otolaryngology should obviously address noise-induced hearing loss. This preventable cause of significant morbidity is underdiagnosed and underrecognized by physicians in general. Thus, it would serve physicians well to highlight the many problems caused by chronic exposure to excessive noise. The pathophysiology and clinical consequences of such exposures are well documented, including the presentation and diagnosis of this condition. Any discussion of noise-induced hearing loss should stress the principles of prevention. Thus, source reduction and history-taking skills should be reinforced in any otolaryngology course. In addition, the upper respiratory tract is frequently the target of environmental and occupational irritants and allergens.

Selected Case Studies From Appendix C

Case No.	Title
11	Chromium Toxicity
19	Lead Toxicity

40	Community Outbreaks of Asthma Associated with Inhalation of Soybean Dust
51	Acoustic Trauma Caused by the Telephone: Report of Two Cases
52	Behavioral and Audiologic Manifestations of Noise-Induced Hearing Loss
54	Childhood Asthma and Indoor Environmental Risk Factors

Pediatrics

Evidence of the profound impact of home environmental factors such as tobacco smoke, lead paint, and poisons on the health of children continues to accumulate. For example, children that experience developmental delay or poor school performance often live in homes and communities with high levels of lead exposure. Their smaller size, developing organ systems, higher respiratory rates, and differing metabolism rates make children particularly susceptible to some agents, including pesticides. In addition, recurrent upper or lower respiratory symptoms in children may signify recurrent or chronic exposure to allergens or irritants such as environmental tobacco smoke, nitrogen oxides from gas stoves, combustion products from inadequately vented wood stoves or space heaters, or agents resulting from home renovation projects.

Selected Case Studies From Appendix C

Case No.	Title
2	Seasonal Arsenic Exposure from Burning Chromium-Copper-Arsenate-Treated Wood
3	Asbestos Toxicity
5	Beryllium Toxicity
13	Dioxin Toxicity
14	Ethylene/Propylene Glycol Toxicity
17	Hantavirus Pulmonary Syndrome: A Clinical Description of 17 Patients with a Newly Recognized Disease
18	Lead Poisoning from Mobilization of Bone Stores During Thyrotoxicosis
19	Lead Toxicity
21	Mercury in House Paint as a Cause of Acrodynia: Effect of Therapy with N-Acetyl-D, L-Penicillamine
22	Mercury Toxicity
26	Fatal Outcome of Methemoglobinemia in an Infant
27	Nitrate/Nitrite Toxicity
28	An Outbreak of Nitrogen Dioxide-Induced Respiratory Illness Among Ice Hockey Players
34	Poisoning of an Urban Family Due to Misapplication of Household Organophosphate and Carbamate Pesticides

Pulmonary Medicine

Current courses in pulmonary medicine usually include a discussion of many environmental and occupational diseases. This is natural since the lung is the portal of entry for all airborne toxicants. Among the competencies that we describe in this report is the knowledge of signs, symptoms, and exposure sources for many agents that produce pulmonary pathology. These include asbestos and agents that cause hypersensitivity pneumonitis. Further, environmental causes of asthma are well-studied, and any discussion of it in a pulmonary medicine course should include a detailed look at the exposure-induced nature of reversible airways disease. Exposure to respiratory irritants is a well-known cause of asthma, and the prevalence of asthma in the general population is increasing. Therefore, using examples of known environmental and occupational causes of the pulmonary disease could serve to make future clinicians more aware of these agents.

Selected Case Studies From Appendix C

Case No.	Title
3	Asbestos Toxicity
5	Beryllium Toxicity
10	Chronic Reactive Airway Disease Following Acute Chlorine Gas Exposure in an Asymptomatic Atopic Patient
11	Chromium Toxicity
12	Cyanide Toxicity
14	Ethylene/Propylene Glycol Toxicity
15	Formalin Asthma in Hospital Staff
17	Hantavirus Pulmonary Syndrome: A Clinical Description of 17 Patients with a Newly Recognized Disease
20	Legionnaires' Disease: Description of an Epidemic of Pneumonia
26	Fatal Outcome of Methemoglobinemia in an Infant
27	Nitrate/Nitrite Toxicity
28	An Outbreak of Nitrogen Dioxide-Induced Respiratory Illness Among Ice Hockey Players
30	Aldicarb Poisoning: A Case Report with Prolonged Cholinesterase Inhibition and Improvement After Pralidoxime Therapy
31	Cholinesterase-Inhibiting Pesticide Toxicity
33	Pesticide Food Poisoning from Contaminated Watermelons in California, 1985
34	Poisoning of an Urban Family Due to Misapplication of Household Organophosphate and Carbamate Pesticides

40	Community Outbreaks of Asthma Associated with Inhalation of Soybean Dust
42	Toluene Toxicity
43	Occupational Asthma Due to Toluene Diisocyanate Among Velcro-Like Tape Manufacturers
54	Childhood Asthma and Indoor Environmental Risk Factors
55	Populations at Risk From Particulate Air Pollution—United States, 1992

Psychiatry

Because of the unusual opportunity for sustained student-patient discussion that occurs on many psychiatry rotations, this clerkship presents a unique opportunity for students to explore the relationship of an individual's work and working conditions to his or her health and happiness. In doing so, students will learn to allow patients to explain aspects of their life, their work, and their home environment—subjects about which they are more expert than the physician. This skill can have ramifications far beyond psychiatry as a discipline, and can reinforce patient-centered holistic approaches to care.

Selected Case Studies From Appendix C

Case No.	Title
8	Carbon Tetrachloride Toxicity
21	Mercury in House Paint as a Cause of Acrodynia: Effect of Therapy with N-Acetyl-D, L-Penicillamine
22	Mercury Toxicity
41	Tetrachloroethylene Toxicity
42	Toluene Toxicity
45	Trimethyltin Encephalopathy
46	Trichloroethylene Toxicity
Appendix A	Taking an Exposure History

Radiology

The lung is the portal of entry for many occupational and environmental toxicants that may affect the lung directly. Various radiographic patterns may be pathognomonic or highly suggestive of specific exposures, while other patterns should at least raise the possibility of an environmental exposure. A clinical radiology rotation is ideal for suggesting differential diagnostic possibilities that include toxic exposure.

Selected Case Studies From Appendix C

Case No.	Title
3	Asbestos Toxicity
5	Beryllium Toxicity
11	Chromium Toxicity
35	Polynuclear Aromatic Hydrocarbon (PAH) Toxicity
38	Radon Toxicity
39	Residential Radon Exposure and Lung Cancer in Sweden

C

Case Studies in Environmental Medicine

This appendix contains 55 case studies from peer reviewed literature, including journal articles and educational material developed by the Agency for Toxic Substances and Disease Registry (ATSDR). They were selected for their clinical interest with respect to environmental factors and health, relevance to particular courses and clerkships in medical school, and illustrative potential for teaching medical school students about the impact of the environment on health.

Four indexes are included in this appendix to help guide the reader in the use of the case studies. Index 1 lists the case studies according to agent or condition (in alphabetical order). Index 2 presents the case studies in terms of the most common medical school courses and clerkships where they might be used. Creative teachers and students, however, may find these case studies helpful in other educational settings and courses/clerkships as well. Index 3 presents the case studies in terms of sentinel pathophysiological conditions, and Index 4 presents the case studies according to common clinical signs, symptoms, and presenting complaints. Taken together, these indexes should help the reader recognize the many opportunities for enhancing knowledge, skills, and abilities in environmental medicine, and integrating an enhancement of environmental medicine in medical education.

The ATSDR case studies included in this appendix are part of a series of self-instructional publications designed to increase the primary provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. Original copies of the ATSDR cases contained in this appendix and others in the series can be obtained from: Continuing Education Coordinator, ATSDR, Division of Health Education (E33), 1600 Clifton Road, N.E., Atlanta, GA 30333.

INDEX 1: Case Studies Related to Chemical Agents and Conditions

Agent	Case Study Title	Case Study No.
Arsenic	*Arsenic Toxicity*	1
	Seasonal Arsenic Exposure from Burning Chromium-Copper-Arsenate-Treated Wood	2
Asbestos	*Asbestos Toxicity*	3
Benzene	*Benzene Toxicity*	4
Beryllium	*Beryllium Toxicity*	5
Cadmium	*Cadmium Toxicity*	6
Carbon Monoxide	*Fetal Death Due to Nonlethal Maternal Carbon Monoxide Poisoning*	7
Carbon Tetrachloride	*Carbon Tetrachloride Toxicity*	8
Chlordane	*Chlordane Toxicity*	9
Chlorine Gas	*Chronic Reactive Airway Disease Following Acute Chlorine Gas Exposure in an Asymptomatic Atopic Patient*	10
Chromium	*Chromium Toxicity*	11
Cyanide	*Cyanide Toxicity*	12
Dioxin	*Dioxin Toxicity*	13
Ethylene/Propylene Glycol	*Ethylene/Propylene Glycol Toxicity*	14
Formalin	*Formalin Asthma in Hospital Staff*	15
Gasoline	*Gasoline Toxicity*	16
Hantavirus	*Hantavirus Pulmonary Syndrome: A Clinical Description of 17 Patients with a Newly Recognized Disease*	17
Lead	*Lead Poisoning from Mobilization of Bone Stores During Thyrotoxicosis*	18
	Lead Toxicity	19
Legionella	*Legionnaires' Disease: Description of an Epidemic of Pneumonia*	20

INDEX 1: Continued

Agent	**Case Study Title**	**Case Study No.**
Mercury	*Mercury in House Paint as a Cause of Acrodynia: Effect of Therapy with N-Acetyl-D, L-Penicillamine*	21
	Mercury Toxicity	22
Methanol	*Methanol Toxicity*	23
Methylene Chloride	*Methylene Chloride Toxicity*	24
	Paint Remover Hazard	25
Nitrates/Nitrites	*Fatal Outcome of Methemoglobinemia in an Infant*	26
	Nitrate/Nitrite Toxicity	27
Nitrogen Dioxide	*An Outbreak of Nitrogen Dioxide-Induced Respiratory Illness Among Ice Hockey Players*	28
Pentachlorophenol	*Pentachlorophenol Toxicity*	29
Pesticides	*Aldicarb Poisoning: A Case Report with Prolonged Cholinesterase Inhibition and Improvement After Pralidoxime Therapy*	30
	Cholinesterase-Inhibiting Pesticide Toxicity	31
	Infertility in Male Pesticide Workers	32
	Pesticide Food Poisoning from Contaminated Watermelons in California, 1985	33
	Poisoning of an Urban Family Due to Misapplication of Household Organophosphate and Carbamate Pesticides	34
Polynuclear Aromatic Hydrocarbon (PAH)	*Polynuclear Aromatic Hydrocarbon (PAH) Toxicity*	35
Polychlorinated Biphenyl (PCB)	*Polychlorinated Biphenyl (PCB) Toxicity*	36
Radiation	*Ionizing Radiation*	37

Appendix C continues

INDEX 1: Continued

Agent	Case Study Title	Case Study No.
Radon	*Radon Toxicity*	38
Radon	*Residential Radon Exposure and Lung Cancer in Sweden*	39
Soybean Dust	*Community Outbreaks of Asthma Associated with Inhalation of Soybean Dust*	40
Tetrachloroethylene	*Tetrachloroethylene Toxicity*	41
Toluene	*Toluene Toxicity*	42
Toluene Diisocyanate	*Occupational Asthma Due to Toluene Diisocyanate Among Velcro-like Tape Manufacturers*	43
1,1,1-Trichloroethane	*1,1,1-Trichloroethane*	44
Trimethyltin	*Trimethyltin Encephalopathy*	45
Trichloroethylene	*Trichloroethylene Toxicity*	46
Vinyl Chloride	*Vinyl Chloride Toxicity*	47

Condition	Case Study Title	Case Study No.
Carpel Tunnel Syndrome	*Work-Related Disorders of the Neck and Upper Extremity*	48
Dermatitis	*Contact Dermatitis in Surgeons from Methylmethacrylate Bone Cement*	49
	Skin Lesions and Environmental Exposures: Rash Decisions	50
Hearing Loss	*Acoustic Trauma Caused by the Telephone: A Report of Two Cases*	51
	Behavioral and Audiologic Manifestations of Noise-Induced Hearing Loss	52

INDEX 1: Continued

Condition	**Case Study Title**	**Case Study No.**
Reproductive and Developmental Effects	*Reproductive and Developmental Hazards*	53
	See also Lead, Pesticides, and Radiation	18, 19, 32, 37
Respiratory Conditions	*Childhood Asthma and Indoor Environmental Risk Factors*	54
	Populations at Risk From Particulate Air Pollution—United States, 1992	55
	See also Chlorine Gas, Formalin, Hantavirus, Legionella, Soybean Dust, and Toluene Diisocyanate	10, 15, 17, 20, 40, 43

Appendix C continues

INDEX 2: Selected Case Studies Related to Common Medical School Courses and Clerkships/Clinical Rotations

Selected Courses	Selected Case Studies
Biochemistry and Physiology	7, 12, 18, 19, 24, 25, 26, 27, 29, 35, 36
Community Medicine/Public Health	17, 20, 30, 31, 32, 33, 34, 38, 39, 40, 54, 55
Epidemiology and Biostatistics	17, 20, 31, 32, 33, 38, 39, 40, 54, 55
Genetics	29, 37, 38
Introduction to Clinical Medicine	See Appendix A
Microbiology	17, 20
Neuroscience	1, 2, 8, 9, 18, 19, 21, 22, 23, 24, 30, 31, 33, 34, 41, 42, 45, 48
Nutrition	2, 6, 18, 33
Pathology	3, 4, 8, 37, 38
Pharmacology	4, 7, 8, 12, 16, 18, 19, 26, 27, 28, 30, 31, 33, 34

Selected Clerkships/Clinical Rotations	Selected Case Studies
Cardiovascular Medicine	7, 12, 19, 23, 24, 25, 26, 27, 29, 30, 31, 33, 34
Dermatology	1, 2, 11, 13, 21, 22, 29, 36, 49, 50
Emergency Medicine	2, 7, 10, 12, 30, 31, 33, 34
Endocrinology	18, 32
Family Medicine	1, 2, 3, 4, 5, 8, 11, 13, 14, 15, 17, 18, 19, 20, 21, 22, 24, 26, 27, 28, 30, 31, 32, 33, 34, 42, 43, 48, 54
Gastrointestinal Disease	8, 11, 18, 27, 30, 31, 33, 34, 36, 47
Hematology/Oncology	3, 4, 11, 13, 18, 19, 26, 35, 37, 38, 39, 46, 47
Infectious Disease	17, 20
Internal Medicine[a]	1, 2, 4, 8, 11, 14, 15, 17, 18, 20, 24, 30, 31, 32, 33, 34, 42, 43, 48

INDEX 2: Continued

Selected Clerkships/Clinical Rotations	Selected Case Studies
Nephrology	1, 2, 6, 8, 14, 18, 19, 21, 22, 23
Neurology	1, 2, 8, 9, 18, 19, 21, 22, 23, 24, 30, 31, 33, 34, 41, 42, 45, 48
Obstetrics-Gynecology[a]	7, 9, 18, 19, 30, 31, 33, 34, 37, 44, 53
Orthopedics	6, 48
Otolaryngology	11, 19, 40, 51, 52, 54
Pediatrics[a,b]	2, 3, 5, 13, 14, 17, 18, 19, 21, 22, 26, 27, 28, 34, 54
Pulmonary Medicine[c]	3, 5, 10, 11, 12, 14, 15, 17, 20, 26, 27, 28, 30, 31, 33, 34, 40, 42, 43, 54, 55
Psychiatry[a]	8, 21, 22, 41, 42, 45, 46 Appendix A
Radiology	3, 5, 11, 35, 38, 39

[a] Required clerkships/clinical rotations in all U.S. medical schools.

[b] Additional information on curriculum content in pediatrics can be found in the Children's Environmental Health Network manual entitled *Kids and the Environment: Toxic Hazards—A Course on Pediatric Environmental Health*. For more information, contact the California Public Health Foundation, Rod Armstrong, The Children's Environmental Health Network, 5900 Hollis Street, Suite E, Emeryville, CA 94608, Telephone (510) 540-3657, Fax (510) 540-2673.

[c] Additional information on curriculum development in pulmonology can be found in the reports:

Preventive Pulmonary Academic Award Program. 1993. Guidelines for Curriculum Development for Undergraduate Medical Education in the Prevention of Pulmonary Diseases. Bethesda, MD: Division of Lung Diseases, National Heart, Lung, and Blood Institute, National Institutes of Health, November.

Preventive Pulmonary Academic Award Program. 1994. Knowledge Bases and Sample Curricula. Bethesda, MD: Division of Lung Diseases, National Heart, Lung, and Blood Institute, National Institutes of Health, March.

Appendix C continues

INDEX 3: Selected Case Studies Related to Sentinel Pathophysiological Conditions for Environmental/Occupational Evaluation

Sentinel Pathophysiological Conditions		Agent or Exposure Discussed	Selected Case Studies
CARDIOVASCULAR	Bradycardia	Pesticide	30, 33
	Chest Pain	Methylene Chloride	24,25
DERMATOLOGIC	Acne	Dioxin	13
	Acne	Polychlorinated Biphenyl (PCB)	36
	Acrodynia	Mercury	22
	Contact Dermatitis	Chromium	11
	Contact Dermatitis	Methylmethacrylate	49
	Hyperkeratosis	Arsenic	1, 2
ENDOCRINOLOGIC	Thyrotoxicosis	Lead	18
GASTROINTESTINAL			
	Abdominal Pain	Lead	18
	Abdominal Pain, Nausea, and Vomiting	Carbon Tetrachloride	8
	Diarrhea	Nitrates	27
	Diarrhea	Pesticides	30, 31, 33, 34
	Vomiting	Pesticides	30, 31, 33, 34
HEMATOLOGIC/ ONCOLOGIC	Hypochronic Anemia	Lead	19
	Leukemia	Benzene	4
	Liver Cancer	Vinyl Chloride	47
	Lung Cancer	Asbestos	3
	Lung Cancer	Polynuclear Aromatic Hydrocarbon (PAH)	35
	Lung Cancer	Radon	39

INDEX 3: Continued

Sentinel Pathophysiological Conditions		Agent or Exposure Discussed	Selected Case Studies
HEMATOLOGIC/ ONCOLOGIC	Methemoglobinemia	Nitrate	26
HEPATIC	Cancer	Vinyl Chloride	47
	Hepatitis	Carbon Tetrachloride	8
	Hepatitis	Polychlorinated Biphenyl (PCB)	36
INFECTIOUS	Respiratory	Hantavirus	17
	Respiratory	Legionella	20
NEUROLOGIC	Ataxia	Mercury	21
	Carpel Tunnel Syndrome (CTS)	Repetitive Motion	48
	Dysarthria	Mercury	21
	Encephalopathy	Trimethyltin	45
	Headache	Carbon Tetrachloride	8
	Headache	Methanol	23
	Headache	Methylene Chloride	24
	Headache	Tetrachloroethylene	41
	Headache	Toluene	42
	Hearing Loss	Lead	19
	Hyperactive	Lead	19
	Peripheral Neuropathy	Arsenic	1, 2
	Tremor	Mercury	21

Appendix C continues

INDEX 3: Continued

Sentinel Pathophysiological Conditions		Agent or Exposure Discussed	Selected Case Studies
OBSTETRIC/GYNECOLOGIC	Miscarriage and Fetal Death	Carbon Monoxide	7
ORTHOPEDIC	Carpel Tunnel Syndrome (CTS)	Repetitive Motion	48
	Osteomalacia Syndrome (CTS)	Cadmium	6
RENAL	Acute Renal Failure	Carbon Tetrachloride	8
	Acute Renal Failure	Ethylene/Propylene Glycol	14
	Acute Renal Failure	Methanol	23
	Chronic Renal Failure	Cadmium	6
	Chronic Renal Failure	Mercury	21, 22
	Chronic Renal Failure	Lead	18, 19
REPRODUCTIVE AND DEVELOPMENTAL	Birth Defects	Various	53
	Birth Defects	Mercury	22
	Birth Defects	Radiation	37
	Developmental Defects	Polychlorinated Biphenyl (PCB)	36
	Developmental Defects	Lead	18, 19
	Infertility	1,2-Dibromo-3-Chloropropane (DBCP)	32
RESPIRATORY	Asthma	Formalin	15
	Asthma	Indoor Environment	54

INDEX 3: Continued

Sentinel Pathophysiological Conditions		**Agent or Exposure Discussed**	**Selected Case Studies**
RESPIRATORY	Chronic Upper Airway	Chromium	11
	Cyanosis	Nitrate	27
	Interstitial Fibrosis	Beryllium	5
	Irritation Symptoms	Chromium	11

SOURCE: Kipen, HM and Craner, J. 1992. Sentinel pathophysiologic conditions: An adjunct to teaching occupational and environmental disease recognition and history-taking. *Environmental Research* 59:93-100.

Appendix C continues

INDEX 4: Selected Case Studies Related to Clinical Signs, Symptoms, and Presenting Complaints

Clinical Signs, Symptoms, and Presenting Complaints	Agent or Exposure Discussed	Selected Case Studies
ABDOMINAL PAIN	Carbon Tetrachloride	8
	Lead	18, 19
	Pesticides	30, 31, 33, 34
ABORTIONS, SPONTANEOUS	Chlordane	9
	1,1,1-Trichloroethane	44
	Various	53
ACNE	Polychlorinated Biphenyl (PCB)	36
ALOPECIA	Arsenic	2
ALTERED MENTAL STATUS WITH UNCONSCIOUSNESS	Arsenic	2
	Carbon Monoxide	7
	Cyanide	12
	Pesticides	30, 31, 33, 34
ANOREXIA	Chlordane	9
	Chromium	11
	Pentachlorophenol	29
	Vinyl Chloride	47
ATAXIA	Mercury	21
	Methanol	23
BIRTH DEFECTS	Reproductive and Developmental Hazards	53
	1,1,1-Trichloroethane	44
BRADYCARDIA	Pesticides	30, 31, 33, 34
CHEST PAIN	Asbestos	3

INDEX 4: Continued

Clinical Signs, Symptoms, and Presenting Conditions	Agent or Exposure Discussed	Selected Case Studies
CHEST PAIN	Methylene Chloride	24, 25
	Nitrogen Dioxide	28
	Toluene Diisocyanate (TDI)	43
CONFUSION	Carbon Tetrachloride	8
	Gasoline	16
	Lead	18, 19
	Methylene Chloride	24
	Pesticides	30, 31, 33, 34
COUGH	Beryllium	5
	Hantavirus	17
	Indoor Environment	54
	Legionella	20
	Nitrogen Dioxide	28
	Radon	39
	Toluene	42
CYANOSIS	Nitrates	27
DELIRIUM	Arsenic	1, 2
	Chromium	11
	Dioxin	13
	Gasoline	16
	Mercury	21, 22
	Methylmethacrylate	49
	Trimethyltin	45
DIFFICULTY CONCENTRATING	Lead	18
	Tetrachloroethylene (TCE)	41

Appendix C continues

INDEX 4: Continued

Clinical Signs, Symptoms, and Presenting Conditions	Agent or Exposure Discussed	Selected Case Studies
DIAPHORESIS	Mercury	21, 22
	Pentachlorophenol	29
	Pesticides	30, 31, 33, 34
DIARRHEA	Carbon Tetrachloride	8
	Hantavirus	17
	Nitrates	26, 27
	Pesticides	30, 31, 33, 34
DYSARTHRIA	Mercury	21
DYSPNEA	Asbestos	3
	Beryllium	5
	Hantavirus	17
	Indoor Environment	54
	Nitrogen Dioxide	28
	Pentachlorophenol	29
	Pesticides	30, 31, 33, 34
	Polynuclear Aromatic Hydrocarbon (PAH)	35
	Toluene	42
	Toluene Diisocyanate (TDI)	43
EPISTAXIS, ECCHYMOSES, and PETECHIA	Arsenic	2
	Benzene	4
	Chromium	11
FATIGUE	Arsenic	2
	Benzene	4
	Lead	18
	Methylene Chloride	24

INDEX 4: Continued

Clinical Signs, Symptoms, and Presenting Conditions	Agent or Exposure Discussed	Selected Case Studies
FATIGUE	Pesticides	30, 31, 33, 34
	Vinyl Chloride	47
FEVER	Hantavirus	17
	Legionella	20
	Pentachlorophenol	29
HEADACHE	Arsenic	2
	Carbon Tetrachloride	8
	Chlordane	9
	Gasoline	16
	Methanol	23
	Methylene Chloride	24
	Nitrogen Dioxide	28
	Pesticides	30, 31, 33, 34
	Tetrachloroethylene (TCE)	41
	Toluene	42
HEARING LOSS	Lead	19
	Occupational Noise	51, 52
HEMOPTYSIS	Nitrogen Dioxide	28
HEPATITIS	Carbon Tetrachloride	8
	Chromium	11
	Polychlorinated Biphenyl (PCB)	36
HEPATOMEGALY	Vinyl Chloride	47
HYPERTENSION	Lead	19
HYPOTENSION	Cyanide	12

Appendix C continues

INDEX 4: Continued

Clinical Signs, Symptoms, and Presenting Complaints	Agent or Exposure Discussed	Selected Case Studies
HYPOTENSION	Pesticides	30, 31, 33, 34
INCONTINENCE	Pesticides	30, 31, 33, 34
INFERTILITY	1,2-Dibromo-3-Chloropropane (DBCP)	32
	Various	53
IRRITABILITY	Gasoline	16
	Mercury	22
	Methylene Chloride	24
	Nitrates	26, 27
	Tetrachloroethylene (TCE)	41
LACRIMATION	Pesticides	30, 31, 33, 34
LOW BACK PAIN	Cadmium	6
MUSCLE TWITCHING	Arsenic	2
	Pesticides	30, 31, 33, 34
MYALGIA	Cadmium	6
	Lead	18
NASAL IRRITATION WITH RHINORRHEA	Chromium	11
NAUSEA	Carbon Tetrachloride	8
	Chlordane	9
	Methanol	23
	Pesticides	30, 31, 33, 34
PERIPHERAL NEUROPATHY	Arsenic	1, 2
	Repetitive Motion	48
PROTEINURIA	Cadmium	6
	Carbon Tetrachloride	8
	Chromium	11

INDEX 4: Continued

Clinical Signs, Symptoms, and Presenting Complaints	Agent or Exposure Discussed	Selected Case Studies
RALES	Asbestos	3
	Pesticides	30, 31, 33, 34
RASH	Arsenic	1, 2
	Chromium	11
	Dioxin	13
	Environmental Exposures (i.e., allergens, irritants)	50
	Mercury	21, 22
	Methylmethacrylate	49
	Pentachlorophenol	29
	Polychlorinated Biphenyl (PCB)	36
SEIZURES	Arsenic	2
	Pesticides	30, 31, 33, 34
	Trimethyltin	45
TACHYCARDIA	Cyanide	12
	Hantavirus	17
	Methanol	23
	Methylene Chloride	24
	Nitrates	26, 27
	Pentachlorophenol	29
TACHYPNEA	Cyanide	12
	Ethylene/Propylene Glycol	14
	Hantavirus	17
	Nitrates	26, 27

Appendix C continues

INDEX 4: Continued

Clinical Signs, Symptoms, and Presenting Complaints	**Agent or Exposure Discussed**	**Selected Case Studies**
TACHYPNEA	Pentachlorophenol	29
TINNITUS	Methanol	23
VISUAL DISTURBANCE	Methanol	23
VOMITING	Carbon Tetrachloride	8
	Ethylene/Propylene Glycol	14
	Hantavirus	17
	Nitrates	26, 27
	Pesticides	30, 31, 33, 34
WEAKNESS	Pesticides	30, 31, 33, 34
	Polynuclear Aromatic Hydrocarbon (PAH)	35
	Repetitive Motion	48
WEIGHT LOSS	Benzene	4
	Chromium	11
	Pentachlorophenol	29
	Polynuclear Aromatic Hydrocarbon (PAH)	35
	Radon	38, 39
	Vinyl Chloride	47
WHEEZING	Formalin	15
	Indoor Environment	54
	Pesticides	30, 31, 33, 34
	Soybean Dust	40
	Toluene Diisocyanate (TDI)	43

ATSDR June 1990

Case Studies in Environmental Medicine

5

Arsenic Toxicity

Environmental ALERT . . .

- ☑ *Except in the electronics industry, the commercial use of arsenic is declining.*
- ☑ *Skin lesions, peripheral neuropathy, and anemia are hallmarks of chronic arsenic ingestion.*
- ☑ *Arsenic is strongly associated with lung and skin cancer in humans, and may cause other cancers as well.*

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. See page 25 for more information about continuing medical education credits and continuing education units.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

A 35-year-old carpenter with peripheral neuropathy and skin lesions

A 35-year-old, fair-skinned male is referred to your clinic for evaluation. His symptoms began approximately 3 months ago, with the insidious onset of numbness and tingling in his toes and fingertips, progressing slowly in the ensuing weeks to involve the feet and hands in a symmetric "stocking-glove" fashion. In the past 2 to 3 weeks, the tingling has taken on a progressively painful, burning quality and he has noted weakness in gripping tools. No ataxia, dysphagia, visual symptoms, or bowel or bladder incontinence have been noted, and he has not complained of headaches, back or neck pain, or confusion. Except as noted, the review of systems is otherwise negative.

The patient's medical history is remarkable for a flu-like illness approximately 4 months ago characterized by 3 to 4 days of fever, cough, diarrhea, and myalgias, which resolved spontaneously.

Further questioning reveals the patient has been a carpenter since completing high school 17 years ago. For the last 10 years, he has lived in a rural, wooded area in a home he built. Approximately 10 months ago he was married and moved with his wife, an elementary school teacher, into a newly built home on an adjacent parcel of land. The patient consumes one to two alcoholic drinks a week, and quit smoking 2 years ago after a 15-pack-year history. He takes one multivitamin a day but no prescription medications. Family history is unremarkable; his wife, parents, and two younger brothers are in good health.

Neurologic examination reveals diminished proprioception in the hands and feet, with a hyperesthetic response to pinprick sensation on the soles. Motor bulk and tone are normal, but there is slight bilateral muscular weakness in dorsiflexors of the toes and ankles, wrist extensors, and hand intrinsics. Reflexes are absent at the ankles and 1+ at the biceps and knees. Coordination and cranial nerve function are within normal limits. Dermatologic examination reveals brown patches of hyperpigmentation, with scattered overlying pale spots in and around the axillae, groin, nipples, and neck. The palms and soles show multiple hyperkeratotic corn-like elevations 4 to 10 mm in diameter. Three irregularly shaped, sharply demarcated, erythematous, scaly plaques, measuring 2 to 3 cm, are noted on the patient's torso. The remainder of the physical examination is normal.

On initial laboratory evaluation, the CBC shows slight macrocytic anemia with hematocrit 35% (normal range 40% to 52%), and MCV 111 fL (normal range 80 to 100 fL). White blood cell count is 4.3 x $10^3/mm^3$ (normal range 3.9 to 11.7 x $10^3/mm^3$); the differential reveals moderate elevation of eosinophils at 9% (normal range 0% to 4%). Occasional basophilic stippling is noted on the peripheral smear. Liver transaminases are slightly elevated. BUN, creatinine, and urinalysis are normal.

Pretest

(a) What problem list is suggested for this patient?

(b) What further investigations would you undertake at this time?

(c) What treatment options would you consider?

Answers to Pretest questions can be found in Challenge answers (2) through (10) on pages 23-24.

1

Exposure Pathways

☐ **Environmental sources of arsenic exposure are food, water, and air.**

☐ **The relative toxicity of an arsenical depends primarily on its chemical type, valence state, solubility, and physical form.**

☐ **Except in the semiconductor industry, commercial use of arsenic has been declining since the 1960s.**

Arsenic is ubiquitous in the environment. It is released into the air by volcanoes, through weathering of arsenic-containing minerals and ores, and by commercial or industrial processes. In industry, arsenic is a byproduct of the smelting process for many metal ores such as lead, gold, zinc, cobalt, and nickel. Other potential sources of arsenic exposure are the following:

Natural Sources

Arsenic-containing mineral ores
Groundwater (especially near geothermal activity)

Commercial Products

Wood preservatives
Pesticides
Herbicides (weed killers, defoliants)
Fungicides
Cotton desiccants
Cattle and sheep dips
Paints and pigments
Anti-fouling paints
Leaded gasoline
Fire salts (multicolored flame)

Food

Wine (grapes sprayed with arsenic-containing pesticides)
Tobacco (plants sprayed with arsenic-containing pesticides)
Seafood (especially bivalves, certain cold water and bottom-feeding finfish, seaweed)

Industrial Processes

Purifying industrial gases (removal of sulfur)
Burning fossil fuels
Burning wood treated with arsenic preservatives
Electronics manufacturing (microwave devices, lasers, light-emitting diodes, photoelectric cells, semiconductor devices)
Hardening metal alloys
Preserving animal hides
Bronze plating
Clarifying glass and ceramics

Medicinals

Fowler's solution
Antiparasitic drugs (carbasone)
Donovan's solution
Folk remedies ("Asiatic pill," *kushtay*, yellow root)
Kelp-containing health foods
Some naturopathic remedies

Arsenic exists in three common valence states: the metalloid (0 oxidation state), arsenite (trivalent state), and arsenate (pentavalent state). Arsenic-containing compounds vary in their toxicity to mammals, depending on valence state, whether it is in the inorganic or organic form, physical state–gas, solution, or powder–and factors such as solubility, particle size, rates of absorption and elimination, and presence of impurities. With few exceptions, inorganic arsenic is more toxic than organic arsenic. The toxicity of trivalent arsenite is typically greater than that of pentavalent arsenate, but little is known about the toxicity of zero valent arsenic. Arsine gas (AsH_3), used mainly in the microelectronics industry, produces a clinical syndrome very different from other arsenic compounds and is the most toxic arsenical.

Until the 1940s, arsenicals (Salvarsan and Fowler's solution) were widely used in the treatment of various diseases such as syphilis and psoriasis. Arsenicals are still used as antiparasitic agents in veterinary medicine, and, in some countries, they are occasionally used to treat trypanosomiasis and amebiasis in humans. Arsenic is also found in some homeopathic and naturopathic preparations, and in folk remedies such as *kushtay*, a tonic used in Asian cultures to cure various sexual disorders.

Commercial use of arsenic peaked in the 1960s and since then has steadily declined. As of 1987, 74% of the arsenic used in the United States is for wood preservation, as compared to less than 1% for semiconductor manufacture. However, commercial use of arsenic in the microelectronics industry is increasing rather than declining. Gallium arsenide (GaAs) is used in integral components of discrete microwave devices, lasers, light-emitting diodes, photoelectric chemical cells, and semiconductor devices. The use of arsine gas (AsH_3) as a dopant in the production of semiconductors is also expected to increase, although substitutes of lower toxicity such as tributylarsine have recently been used. A source of arsine exposure is accidental release while manufacturing, transporting, or using the gas. More often, however, arsine forms unexpectedly when acid or other reducing substances are added to arsenic-containing compounds, such as metals in which arsenic is a low-level contaminant.

In the general population, the main route of arsenic exposure is via ingestion of arsenic-containing food and water. It has been estimated that the average daily dietary intake of arsenic by adults in the United States is 50 micrograms (µg) per day (range of 8 to 104 µg), of which about 18 µg is inorganic arsenic. Meat, fish, and poultry account for 80% of dietary arsenic intake. Fish, seafood, and algae also contain high concentrations of arsenic in the form of arsenobetaine and arsenocholine, sometimes referred to as "fish arsenic." Fish arsenic has low toxicity to humans and is rapidly excreted in urine. Wine made from grapes sprayed with arsenic-containing pesticides may have appreciable levels of arsenic. Smokers may also inhale small amounts of arsenic as a result of pesticide residue on tobacco leaves.

Well water contaminated by natural sources such as arsenic-containing bedrock has been reported to be the cause of arsenic toxicity throughout the world, including areas of the United States, Germany, Argentina, Chile, Taiwan, and the United Kingdom. The areas in the United States with the highest natural groundwater concentrations of arsenic are the Southwest, Northwest, Alaska, and other areas near geothermal activity. Groundwater may also contain elevated concentrations of arsenic due to contamination from arsenical pesticide runoff. A study conducted in 1970 reported that up to 1% of community water supplies in the United States had arsenic concentrations exceeding 10 ppb. (The U.S. Environmental Protection Agency's [EPA] proposed maximum contaminant level for arsenic in drinking water is 50 parts per billion [ppb].) Both the trivalent and pentavalent forms of inorganic arsenic can be found in drinking water.

Challenge

(1) The patient described in the case study lives in the wooded foothills of the Cascade range in northwest Washington. His activities have consisted mainly of building new wood frame housing, with occasional renovation of older structures. He has used lumber from these projects to fuel the stove and fireplaces in his home. Drinking water is obtained from an artesian well located on his property.

What are the potential sources of arsenic exposure for the patient described in the case study?

(2) What steps can be undertaken to identify sources of the patient's arsenic exposure?

Who's At Risk

- ☐ **Workers in industries producing or using arsenic-containing compounds are potentially at risk.**
- ☐ **Persons whose water supply contains high levels of arsenic or those living near sources of high ambient air levels of arsenic are at increased likelihood of exposure.**

The quantity of arsenic released by human activities exceeds amounts released from natural sources at least threefold. The major sources of arsenic release to the environment are smelters and pesticides. Besides refinery workers and farmers, other workers at increased risk of arsenic exposure include those in the industries listed on page 2. People living near smelters and other arsenic-emitting facilities also have potential risk of exposure from fugitive airborne emissions and groundwater contamination.

Arsenic is notorious as a poison because white arsenic (arsenic trioxide) has no odor or taste and is available in inexpensive products such as pesticides. Most arsenic poisonings are due to unintentional ingestion by children. In 1989, EPA instituted a phaseout of certain arsenic-containing ant poisons in an effort to reduce the incidence of children's arsenic ingestion.

Burning plywood treated with an arsenate wood preservative in a poorly ventilated cabin has been blamed for poisoning a family in rural Wisconsin. Green wood or pressed wood treated with copper arsenate to prevent mildew is commonly used in marine applications, patio decks, and recreational structures for children's playgrounds. Cutting this wood or erosion of the veneer may lead to arsenic exposure. Children who play on wood structures treated with copper arsenate have increased likelihood of dermal contact or ingestion of the arsenical through normal mouthing and play activities.

Methyl transferase enzymes play a necessary role in the methylation of arsenic in mammals. The effect of dietary deficiencies and genetic variability on methylating capacity may have important implications for tissue distribution and individual susceptibility to arsenic toxicity. Experimental animals fed protein-deficient diets while exposed to high levels of arsenic have shown a decreased methylating capacity, which has led to increased deposits of arsenic in liver, lung, and other organ sites, and presumably increased susceptibility to arsenic toxicity.

Arsenic can cross the placenta, exposing the fetus. Significant levels of arsenic were found in an infant born 4 days after the mother ingested arsenic in a suicide attempt. Increased incidence of spontaneous abortions, infant congenital malformations, and decreased birth weights have been reported among women and their offspring living near a smelter in Sweden; however, it is not clear that these events can be ascribed to arsenic alone.

☐ **Arsenic can cross the placenta, increasing the likelihood of exposure to the fetus.**

Biologic Fate

☐ **The primary routes of arsenic entry into the human body are ingestion and inhalation; percutaneous absorption has been reported in occupational settings.**

☐ **Most tissues rapidly clear arsenic except for skin, hair, and nails.**

In humans, soluble forms of ingested arsenic are well absorbed from the gastrointestinal tract (60% to 90%). The amount of arsenic absorbed by inhalation has not been determined precisely, but is thought to be in this range. Dermal absorption is generally negligible, although toxic systemic effects have resulted from rare occupational accidents where either arsenic trichloride or arsenic acid was splashed on workers' skin. Airborne arsenic in the workplace is generally in the form of arsenic trioxide. Its particle size determines whether arsenic will reach

- ☐ **Arsenic undergoes biomethylation to less toxic metabolites in the liver.**
- ☐ **Arsenic is excreted in the urine; most of a single, low-level dose is excreted within a few days after ingestion.**

the lower respiratory tract or be deposited in the upper airways and be swallowed after mucociliary clearance. Autopsies performed on retired smelter workers show that arsenic-containing particles may remain in the lungs for years.

After absorption through the lungs or gastrointestinal tract, arsenic initially accumulates in the liver, spleen, kidney, lungs, and gastrointestinal tract. Clearance from these tissues, however, is rapid. Two to 4 weeks after exposure ceases, most of the arsenic remaining in the body is found in keratin-rich tissues such as skin, hair, and nails, and to a lesser extent, in bones and teeth.

Oxidation-reduction reactions result in some interconversion of arsenate (+5) and arsenite (+3) *in vivo*. A portion of the arsenite is then biomethylated, predominantly in the liver, to methylarsonic acid and dimethylarsinic acid. The methylation process may represent detoxification because the metabolites exert less acute toxicity in experimental lethality studies.

Methylation efficiency in humans decreases with increasing arsenic dose. When the methylating capacity of the liver is exceeded, exposure to excess levels of inorganic arsenic results in increased retention of arsenic in soft tissues. Cell culture studies suggest that the methylating process is inducible since pretreatment with small amounts of arsenic over a prolonged period increases the methylating efficiency when a large dose is subsequently applied. Fish arsenic is apparently not biotransformed *in vivo*, but is rapidly excreted unchanged in the urine.

Arsenic is excreted primarily through the kidneys. After low-level exposure to inorganic arsenic, most of the urinary arsenic is present as methylated metabolites. Other less important routes of elimination of inorganic arsenic include sweat, skin desquamation, and incorporation into hair and nails.

After a single intravenous injection of radiolabeled trivalent inorganic arsenic in human volunteers, most of the arsenic cleared through urinary excretion within 2 days, although a small amount of arsenic was found in the urine up to 2 weeks later. The biologic half-life of ingested fish arsenic in humans is estimated to be less than 20 hours, with total clearance in approximately 48 hours. Because arsenic is rapidly cleared from the blood, blood levels may be normal even when urine levels remain markedly elevated.

Challenge

(3) Analysis of a spot sample of the patient's urine revealed 6000 µg/L (normal is less than 50 µg/L) as total arsenic. What factors could be responsible for this level, and what additional history would you elicit?

Physiologic Effects

Two mechanisms of arsenic toxicity that may lead to injury in a number of organ systems have been described. It is believed that arsenic's overt toxicity results primarily from its inhibition of critical sulfhydryl-containing enzymes; trivalent arsenite is particularly potent in this regard. Pentavalent arsenate, however, can competitively substitute for phosphate in many biochemical reactions. Replacing the stable phosphate anion with the less stable arsenate anion leads to rapid hydrolysis of the high-energy bonds in compounds such as ATP. Loss of these bonds results in the loss of energy needed for critical steps in cellular metabolism.

Arsine gas poisoning results in a considerably different syndrome from that caused by other forms of arsenic. After inhalation, arsine rapidly fixes to red cells, producing irreversible cell membrane damage. At low levels arsine is a potent hemolysin, causing dose-dependent intravascular hemolysis. At high levels arsine produces direct multisystem cytotoxicity.

- ☐ **Because it targets ubiquitous enzyme reactions, arsenic affects nearly all organ systems.**
- ☐ **Unlike other arsenicals, arsine gas causes a hemolytic syndrome.**
- ☐ **Arsenic is strongly associated with lung and skin cancers and may cause other cancers.**

Gastrointestinal, Hepatic, and Renal Effects

The gastrointestinal effects of arsenic are generally the result of ingestion; however, GI effects may also occur after heavy exposure by other routes. The fundamental GI lesion appears to be increased permeability of the small blood vessels, leading to fluid loss and hypotension. Extensive inflammation and necrosis of the mucosa and submucosa of the stomach and intestine

- ☐ **Gastrointestinal effects are seen primarily after arsenic ingestion, and less often after inhalation or dermal absorption.**

may occur and progress to perforation of the gut wall. A hemorrhagic gastroenteritis may develop, with bloody diarrhea as a presenting symptom.

- ☐ **Acute arsenic toxicity may be associated with hepatic necrosis and elevated levels of liver enzymes.**
- ☐ **Arsenic is capable of causing acute renal failure, as well as chronic renal insufficiency.**

Arsenic intoxication may also result in hepatic effects, including elevated liver enzyme levels. Autopsies of Japanese children poisoned with arsenic-contaminated milk revealed hepatic hemorrhagic necrosis and fatty degeneration of the liver. Chronic arsenic ingestion may lead to noncirrhotic portal hypertension. Case reports have also linked chronic high-level arsenic exposure with hepatic angiosarcoma, a rare form of cancer.

The systemic toxicity occurring in severe acute arsenic poisoning may be accompanied by acute renal tubular necrosis. Glomerular damage can result in proteinuria. Cortical necrosis has also been reported.

Cardiovascular Effects

- ☐ **Acute arsenic poisoning may cause both diffuse capillary leak and cardiomyopathy, resulting in shock.**
- ☐ **Long-term ingestion of arsenic in drinking water has resulted in pronounced peripheral vascular changes.**

The extent of cardiovascular injury may vary with age, arsenic dose, and individual susceptibility. In acute arsenic poisoning–usually suicide attempts–the fundamental lesion, diffuse capillary leak, leads to generalized vasodilation, transudation of plasma, hypotension, and shock. Delayed cardiomyopathy may also develop. Myocardial damage can result in a variety of electrocardiographic findings including broadening of the QRS complex, prolongation of the QT interval, ST depression, flattening of T waves, and atypical, multifocal ventricular tachycardia.

Epidemiologic evidence indicates that chronic arsenic exposure is associated with vasospasm and peripheral vascular insufficiency. Gangrene of the extremities, known as Blackfoot disease, has been associated with drinking arsenic-contaminated well water in Taiwan, where the prevalence of the disease increased with increasing age and well-water arsenic concentration (10 to 1820 ppb). Persons with Blackfoot disease also had a higher incidence of arsenic-induced skin cancer. However, investigators believe other vasoactive substances found in the water may have been contributory.

Raynaud's phenomenon and acrocyanosis resulted from contamination of the city's drinking water supply in Antofagasta, Chile, at arsenic concentrations ranging from 20 to 400 ppb. Autopsies of Antofagasta children exposed to arsenic revealed fibrous thickening of small- and medium-sized arteries and myocardial hypertrophy. Similar vascular disorders, as well as abnormal electrocardiographs (ECGs), have been noted in vineyard workers exposed to arsenical pesticides.

Neurologic Effects

Peripheral neuropathy is a common complication of arsenic poisoning. It is predominantly due to destruction of axonal cylinders (axonopathy). Early electrodiagnostic testing may reveal features indistinguishable from Guillain-Barré syndrome (acute inflammatory demyelinating polyneuropathy). The neuropathy evolves into a more classic sensorimotor distal axonopathy. Sensory effects, particularly painful dysesthesia, occur earlier and may predominate in moderate poisoning, whereas ascending weakness and paralysis may predominate in severe poisoning. However, cranial nerves are rarely affected, even in severe poisoning. Both acute and chronic arsenic intoxication may be associated with encephalopathy.

Recovery from neuropathy induced by chronic exposure to arsenic compounds is generally slow, sometimes taking years, and complete recovery may not occur. Follow-up studies of Japanese children who chronically consumed arsenic-contaminated milk revealed an increased incidence of severe hearing loss, mental retardation, epilepsy, and other brain damage. Hearing loss as a sequelae of acute or chronic arsenic intoxication has not been confirmed by other case reports or epidemiologic studies.

☐ **Arsenic-exposed patients develop destruction of axonal cylinders leading to peripheral neuropathy.**

Dermal Effects

The skin lesions occurring most frequently in arsenic-exposed humans are hyperpigmentation, hyperkeratosis, and skin cancer. Patchy hyperpigmentation, a pathologic hallmark of chronic exposure, may be found anywhere on the body, but occurs particularly on the eyelids, temples, axillae, neck, nipples, and groin. The classic appearance of the dark brown patches with scattered pale spots is sometimes described as "raindrops on a dusty road." In severe cases, the pigmentation extends broadly over the chest, back, and abdomen. Pigment changes have been observed in populations chronically consuming drinking water containing 400 ppb or more arsenic.

Arsenical hyperkeratosis occurs most frequently on the palms and soles. Keratoses usually appear as small corn-like elevations, 0.4 to 1 centimeter in diameter. In most cases, arsenical keratoses show little cellular atypia and may remain morphologically benign for decades. In other cases, cells develop marked atypia (precancerous) and appear indistinguishable from Bowen's disease, which is an *in situ* squamous cell carcinoma discussed in Carcinogenic Effects below.

☐ **Pigment changes and palmoplantar hyperkeratosis are characteristic of chronic arsenic exposure.**

☐ **Benign arsenical keratoses may progress to malignancy.**

Respiratory Effects

☐ **Inhalation of high concentrations of arsenic compounds produces irritation of the respiratory mucosa.**

☐ **Lung cancer has been reported in populations of arsenic-exposed smelter workers.**

Smelter workers experiencing prolonged exposures to high concentrations of airborne arsenic at levels rarely found today had inflammatory and erosive lesions of the respiratory mucosa, including nasal septum perforation. Lung cancer has been associated with chronic arsenic exposure in smelter workers and pesticide workers.

Hematopoietic Effects

☐ **Bone marrow depression may result from acute or chronic arsenic intoxication and may initially manifest as pancytopenia.**

Both acute and chronic arsenic poisoning may affect the hematopoietic system. A reversible bone marrow depression with pancytopenia may occur. Anemia and leukopenia are common in chronic arsenic toxicity and are often accompanied by thrombocytopenia and mild eosinophilia. The anemia may be normocytic or macrocytic, and basophilic stippling may be noted on peripheral blood smear.

Carcinogenic Effects

☐ **The carcinogenicity of arsenic in humans has been established, but no animal model has been developed.**

In humans, chronic arsenic ingestion is strongly associated with an increased risk of skin cancer, and may cause cancers of the lung, liver, bladder, kidney, and colon; chronic inhalation of arsenicals has been closely linked with lung cancer. The precise mechanism of arsenic-related carcinogenicity is unknown. Arsenic causes chromosomal damage in cultured mammalian cells, which may be mediated by arsenic's effects on the enzymatic processes involved in DNA replication and repair. Paradoxically, cancer associated with arsenic exposure has not been produced in experimental animals.

Skin Cancer

☐ **Latency for skin cancer associated with ingestion of arsenic may be 3 to 4 decades, while the noncarcinogenic skin effects typically develop several years after exposure.**

An increased risk of skin cancer in humans is associated with chronic exposure to inorganic arsenic in medication, contaminated water, and the workplace. Arsenic-induced skin cancer is frequently characterized by lesions over the entire body, mostly in unexposed areas such as the trunk, palms, and soles. More than one type of skin cancer may occur in a patient. Most of the Taiwanese who developed skin cancer in association with ingested arsenic-contaminated drinking water had multiple cancer types. The most commonly reported types, in order of decreasing frequency, were intraepidermal carcinomas (Bowen's disease), squamous cell carcinomas, basal cell carcinomas, and "combined forms." Seventy-two percent of the Taiwanese with skin cancer also had hyperkeratosis, and 90% had hyperpigmentation.

Some hyperkeratinized lesions can develop into intraepidermal carcinoma, which may ultimately become invasive. The lesions are sharply demarcated, round or irregular plaques that tend to enlarge; they may vary in size from 1 mm to more than 10 cm. Arsenical basal cell carcinomas most often arise from normal tissue, are almost always multiple, and frequently occur on the trunk. The superficial spreading lesions are red, scaly, atrophic, and are often indistinguishable from Bowen's disease by clinical examination. Arsenic-associated squamous cell carcinomas are distinguished from uv-induced squamous cell carcinomas by their tendency to occur on the extremities (especially palms and soles) and trunk rather than on sun-exposed areas such as the head and neck.

Epidemiologic studies indicate that a dose-response relationship exists between the level of arsenic in drinking water and the prevalence of skin cancers in the exposed population. Excessive mortality rates due to arsenic-induced skin cancer have also been observed in vineyard workers with dermal and inhalation exposure.

Lung Cancer

An association between lung cancer and occupational exposure to inorganic arsenic has been confirmed in several epidemiologic studies. A higher risk of lung cancer was found among workers exposed predominantly to arsenic trioxide in smelters and to pentavalent arsenical pesticides in other settings. Neither concomitant exposure to sulfur dioxide nor cigarette smoke were determined to be essential co-factors in these studies.

☐ **In arsenic-exposed workers, there is a systematic gradient in lung cancer mortality rates, depending upon duration and intensity of exposure.**

Clinical Evaluation

History and Physical Examination

The source of exposure is identified in fewer than 50% of arsenic poisonings; however, a careful history and physical examination may improve these statistics. Because arsenic intoxication may affect multiple organ systems, a complete physical examination is imperative. In chronic ingestion, particular clues to arsenic

☐ **The source of arsenic exposure cannot be identified in many cases.**

poisoning may be provided by dermatologic and neurologic findings. The medical history should include the following:

- occupational history
- diet
- residential history (proximity to smelters, other industry, and hazardous waste sites)
- smoking history
- condition of household pets
- hobbies (including use of pesticides or herbicides in farming or gardening)
- medications (including folk or naturopathic medications)
- source of drinking water
- home heating methods (wood-burning stoves and fireplaces)

Signs and Symptoms

Acute Exposure

Acute arsenic poisoning rarely occurs in the workplace today; it usually results from unintentional ingestion, suicide, or homicide. The fatal dose of ingested arsenic in humans is difficult to determine from case reports and depends upon many factors (e.g., solubility, valence state, etc.). The minimal lethal dose is in the range of 50 to 300 milligrams. The signs and symptoms of acute arsenic poisoning include the following:

☐ **In acute arsenic poisoning, death is usually due to cardiovascular collapse and hypovolemic shock.**

☐ **Onset of peripheral neuropathy may be delayed several weeks after the initial toxic insult.**

☐ **Mees lines may be visible in the fingernails several months after acute arsenic exposure.**

Gastrointestinal

- severe abdominal pain
- nausea and vomiting
- bloody or rice-water diarrhea

Neurologic

- light-headedness
- headache
- weakness, lethargy
- delirium
- encephalopathy
- convulsions
- coma
- sensorimotor peripheral neuropathy

Other

- rhabdomyalysis
- garlic odor on the breath
- delayed appearance of Mees lines

Cardiovascular and Respiratory

- hypotension, shock
- ventricular arrhythmia
- pulmonary edema

Hepatic and Renal

- elevated liver enzymes
- hematuria, oliguria, proteinuria,
- acute tubular necrosis, renal cortical necrosis

Hematologic

- anemia
- leukopenia
- thrombocytopenia
- disseminated intravascular coagulation

As a result of inorganic arsenic's direct toxicity to the epithelial cells of the gastrointestinal tract and its systemic enzyme inhibition, profound gastroenteritis, sometimes with hemorrhage, can occur within minutes to hours after acute ingestion. Symptoms may last for several days. Difficulty in swallowing, abdominal pain, vomiting, diarrhea, and dehydration may result. However, in subacute poisoning the onset of milder GI symptoms may be so insidious that the possibility of arsenic intoxication is overlooked.

Arsenic has deleterious effects on the heart and peripheral vascular system. Capillary dilation with fluid leakage and third spacing may cause severe hypovolemia and hypotension. Cardiac manifestations have included cardiomyopathy, ventricular dysrhythmias (atypical ventricular tachycardia and ventricular fibrillation), and congestive heart failure.

A delayed sensorimotor peripheral neuropathy may occur after acute arsenic poisoning. Symptoms are initially sensory and may begin 2 to 4 weeks after resolution of the first signs of intoxication resulting from ingestion (shock or gastroenteritis). Commonly reported initial symptoms include numbness, tingling and "pins and needles" sensations in the hands and feet in a symmetrical "stocking-glove" distribution, and muscular tenderness in the extremities. Clinical involvement spans the spectrum from mild paresthesia with preserved ambulation to distal weakness, quadriplegia, and, in rare instances, respiratory muscle insufficiency.

Other findings in acute arsenic poisoning may include fever and facial edema. Several months after poisoning, transverse white striae (pale bands) on the nails called Mees lines (or Aldrich-Mees lines) may be seen, reflecting transient disruption of nail plate growth during acute poisoning. In episodes of multiple acute exposures, several Mees lines may occur within a single nail. In some cases, the distance of the lines from the nail bed may be used to roughly gauge the date of the poisoning episode.

Respiratory tract irritation (cough, laryngitis, mild bronchitis, and dyspnea) may result from acute exposure to airborne arsenic dust. Nasal septum perforation, as well as conjunctivitis and dermatitis, have also been reported.

The toxicity of arsine gas is quite different from toxicity of other arsenicals, requiring different emphases in the medical history, physical examination, and patient management. Arsine is a powerful hemolytic poison in both acute and chronic exposures. The clinical signs of hemolysis may not appear for up to 24 hours after acute exposure, thereby obscuring the relationship between exposure and effect. Initial symptoms of arsine poisoning may include headache, nausea, abdominal pain, and hematuria.

Chronic Exposure

☐ **Neuropathy may be the first sign of chronic arsenic toxicity.**

☐ **Hyperpigmentation and hyperkeratosis are delayed hallmarks of chronic arsenic exposure.**

☐ **Anemia often accompanies skin lesions in patients chronically poisoned by arsenic.**

☐ **Lung cancer and skin cancer are serious long-term concerns in cases of chronic arsenic exposure.**

Skin lesions and peripheral neuropathy are the most suggestive effects of arsenic ingestion, and their presence should result in an aggressive search for this etiology. Neuropathy can occur insidiously in chronic toxicity without other apparent symptoms. However, careful evaluation usually reveals signs of multiorgan and multisystem involvement such as anemia, leukopenia, skin changes, or elevated liver function tests.

Manifestations of chronic arsenic ingestion depend on both the intensity and duration of exposure. An intense exposure of several milligrams a day results in anemia, neuropathy, and hepatotoxicity within a few weeks to months. Hematologic and neurologic signs may occur after a similar latency period. Skin lesions, however, take longer to manifest (3 to 7 years for pigmentation changes and keratoses; up to 40 years for skin cancer) and may occur after lower doses than those causing neuropathy or anemia.

Chronic arsenic dust inhalation may be accompanied by upper respiratory symptoms, nasal perforation, and lung cancer; however, since permissible workplace arsenic levels have been lowered, these conditions are rarely encountered in workers.

Challenge

(4) What findings are suggestive of arsenic intoxication in the patient described in the case study?

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(5) What conditions other than arsenic intoxication should be considered in the differential diagnosis of the patient's neurological complaints?

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Laboratory Tests

Clinical diagnosis of arsenic intoxication is often difficult because both acute and chronic poisoning present a wide spectrum of signs and symptoms, which are largely dependent upon route of exposure, chemical form, dose, and time elapsed since exposure. In many cases, the patient or person providing the history may suppress information, or the source of exposure may not be apparent. By integrating laboratory results with history and clinical findings, it is often possible to confirm a diagnosis.

☐ **Early clinical diagnosis of arsenic toxicity is often difficult; a key laboratory test in recent exposures is urinary arsenic excretion.**

Immediately after patient stabilization, laboratory tests should be performed to obtain baseline values, with periodic monitoring as indicated. Because urinary levels of arsenic may drop rapidly in the first 24-48 hours after acute exposure, a urine specimen for arsenic analysis should be obtained promptly. Depending on the patient's clinical state, tests may include the following:

General Tests
- CBC with peripheral smear
- Liver function tests
- BUN and creatinine
- Urinalysis
- Nerve conduction velocity (if peripheral neurologic symptoms are present)
- ECG
- Chest X ray
- Bone marrow biopsy

Specific Tests
- Urine arsenic concentration

Some arsenic compounds, particularly those of low solubility, are radiopaque, and if ingested may be visible on an abdominal radiograph.

Direct Biologic Indicators

☐ **When total urinary arsenic is measured, it is important to inquire about recent diet.**

The key diagnostic laboratory test for recent exposure is urinary arsenic measurement. The best specimen is a 24-hour urine collection, although spot urine specimens can be helpful in an emergency. Normal total urinary arsenic values are less than 50 µg arsenic per liter (As/L) in the absence of consumption of seafood in the past 48 hours; values in excess of 200 µg As/L are considered abnormal. Test results may be reported in µg arsenic per gram creatinine to avoid effects due to variation in urine output. Fish arsenic can significantly increase total urinary arsenic levels; therefore, it may be prudent to take a dietary history of the previous 48 hours or repeat the urinary arsenic test in 2 or 3 days. Human volunteers with an average pretest urinary arsenic level of 30 µg/L were given lobster tail for lunch. Four hours after eating, they had an average urinary level of 1300 µg As/L. These values decreased to pretest levels within 48 hours after ingestion. Arsenic blood levels, normally less than 7 µg/dL, are less useful than urinary arsenic measurements in following the clinical course of an acute poisoning case because of the rapid clearance of arsenic from the blood.

Long after urine levels have returned to baseline, the arsenic content of hair and nails may be the only clue of arsenic exposure. However, because the arsenic content of hair and nails may be increased by external contamination, caution must be exercised in using the arsenic content of these specimens to diagnose arsenic intoxication.

Indirect Biologic Indicators

The standard tests listed above will aid in evaluating the status of an arsenic-exposed patient. The CBC can provide evidence of arsenic-induced anemia, leukopenia, thrombocytopenia, or eosinophilia. Although basophilic stippling on the peripheral smear does not confirm arsenic poisoning, it is consistent with the diagnosis. Liver transaminases are frequently elevated in acute and chronic arsenic exposure and can help confirm clinical suspicion. If arsenic neuropathy is suspected, nerve conduction velocity tests should be performed. Such tests may show a decrease in amplitude initially, as well as slowed conduction. Skin lesions in patients with chronic arsenic exposure may require biopsy to rule out skin cancer.

Challenge

(6) What further medical work-up is indicated for the patient described in the case study?

(7) What does the presence of palmar-plantar keratosis suggest about the time course of the patient's arsenic exposure?

(8) Who else in the case study is at risk for exposure to arsenic?

(9) A urine specimen from the wife of the patient was found to contain total arsenic at a concentration of 300 µg/L, and a sample of the wife's hair contained 150 ppm arsenic. Compare this to the patient's 6000 µg/L urinary arsenic level and 100 ppm arsenic in the hair. The wife has no signs or symptoms of chronic arsenic intoxication. How might these findings be explained?

Treatment and Management

Acute Exposure

Patients with suspected acute arsenic poisoning generally require rapid stabilization with fluid and electrolyte replacement in an intensive-care setting. Aggressive intravenous fluid replacement therapy may be life-saving in severe acute poisoning. Gastric lavage may be useful soon after an acute ingestion to prevent further absorption. The efficacy of activated charcoal is controversial, but its administration together with a cathartic (such as sorbitol) is frequently recommended. If profuse diarrhea is present, cathartics should be withheld. Hemodialysis may be beneficial in a patient with concomitant renal failure.

☐ **Gut decontamination and hemodynamic stabilization are key factors in the initial management of acute arsenic intoxication.**

☐ **Chelating agents administered within hours of arsenic absorption may successfully prevent the full effects of arsenic toxicity.**

Dimercaprol (2,3-dimercaptopropanol, also known as British anti-Lewisite or BAL) is the most frequently recommended chelating agent for arsenic. Parenteral dimercaprol is often administered intramuscularly at an initial dose of 3 to 5 milligrams per kilogram of body weight every 4 hours for 2 days, and every 6 hours on the third day, then every 12 hours thereafter for 10 days, unless an orally administered chelating agent is substituted. Data supporting duration of treatment are limited, and regimens may warrant adjustment. If acute renal insufficiency develops, hemodialysis may be of value in removing the dimercaprol-arsenic complex. Since certain dimercaprol-metal complexes are less stable in acid media, alkalization of the urine has been recommended to protect the kidneys during therapy. All known chelating agents have adverse side effects and should be used with caution.

In animal models, the efficacy of chelation therapy generally declines as the time elapsed since exposure increases. If patients are treated within several hours after arsenic ingestion, chelation is likely to be beneficial. Therefore, even if arsenic ingestion is only suspected, it may be valuable to give one or two doses of dimercaprol while awaiting confirmation since side effects usually are not noxious enough to outweigh benefits.

Another potential chelating agent is dimercaptosuccinic acid (DMSA), a water-soluble analog of dimercaprol currently under investigation. Hypotension, nausea, vomiting, and diarrhea early in the course of arsenic poisoning may hamper administration and subsequent absorption of oral DMSA. The use of D-penicillamine as an oral chelating agent is controversial.

Therapy in arsine gas poisoning is supportive and is primarily aimed at maintaining renal function. Exchange transfusion with donor cells may be necessary to replace the patient's hemolyzed red cells.

If the source of arsenic exposure has not been determined, it may be inadvisable to discharge patients until the health department or other appropriate officials have inspected their environment. Unless such inspection locates and eliminates the source of exposure, the patient may be at risk for further arsenic intoxication.

Chronic Exposure

Identification and removal of the toxic source and supportive measures are primary concerns for the treatment of chronically exposed patients. Studies suggest that the use of vitamin A analogs (retinoids) may be useful in treating precancerous arsenical dermatoses. Recovery from chronic arsenic toxicity, particularly from the resulting peripheral neuropathy, may take months and may not be complete. An established arsenical neuropathy is not improved by chelation therapy. The value of chelation therapy in preventing an incipient neuropathy has been suggested but not adequately demonstrated.

- ☐ **Removal from the source of poisoning and supportive measures are used to manage a patient chronically poisoned with arsenic.**
- ☐ **Available evidence does not support the routine use of chelation therapy for patients with an established arsenic neuropathy.**

Challenge

(10) What treatment will you recommend for the patient described in the case study?

Standards and Regulations

Workplace

Air

The Occupational Safety and Health Administration (OSHA) mandates permissible limits for occupational exposures. The permissible exposure limit (PEL) for arsenic can be no greater than 10 micrograms of inorganic arsenic per cubic meter of air (10 μg/m^3), averaged over any 8-hour period for a 40-hour work-week. The recommended exposure limit (REL) set by the National Institute for Occupational Safety and Health (NIOSH), is 2 μg/m^3 for a 15-minute ceiling, based on classification of arsenic as a potential human carcinogen (Table 1).

☐ **There is little agreement between governmental regulations and the recommendations of advisory organizations on the acceptable levels of arsenic in the workplace.**

Table 1. Standards and regulations for inorganic arsenic

Agency *	Focus	Level	Comments
ACGIH	Air-Workplace	200 μg/m^3	Advisory; 8-hour TWA†
NIOSH	Air -Workplace	2 μg/m^3	Advisory; 15-min ceiling limit
OSHA	Air -Workplace	10 μg/m^3	Regulation; PEL§ over 8-hour workday
EPA	Air-Environment	N/A	Under review
	Water	50 ppb	Regulation; maximum contaminant level in drinking water
FDA	Food	0.5-2 ppm	Regulation; applies to animals treated with veterinary drugs

[*] ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; WHO = World Health Organization

[†] TWA (Time-Weighted Average) = time-weighted average concentration for a normal 8-hour workday and 40-hour workweek to which nearly all workers may be repeatedly exposed.

[§] PEL (Permissible Exposure Limit) = highest level averaged over an 8-hour workday, to which a worker may be exposed.

Environment

Air

- **EPA limits the emissions from copper smelters, glass manufacturing plants, and other arsenic-using facilities; however, no ambient air standard for arsenic currently exists.**

Arsenic is listed by EPA, under authorization of the Clean Air Act, as a hazardous air pollutant, defined as a substance that may cause an increased mortality or serious illness in humans after significant exposure. In 1986, EPA promulgated the National Emissions Standards for Hazardous Air Pollutants for three stationary source categories known to emit organic arsenic: primary copper smelters, glass manufacturing plants, and arsenic plants. However, there is currently no ambient air standard for arsenic.

Drinking Water

- **EPA has recently proposed 50 ppb as the allowable level for arsenic in drinking water.**

The EPA Office of Drinking Water has proposed a MCL for arsenic in drinking water of 50 ppb. The World Health Organization (WHO) also recommends a drinking water guideline of 50 ppb, which is considered to be a tenfold safety margin above levels known to have caused skin cancer in Taiwan.

Food

- **FDA currently has no tolerance levels for arsenic in food, except for the byproducts of animals treated with veterinary drugs.**

The U.S. Food and Drug Administration (FDA) has established tolerance levels for arsenic in byproducts of animals treated with veterinary drugs. These permissible levels range from 0.5 ppm in eggs and uncooked edible tissues of chickens and turkeys to 2 ppm in certain uncooked edible byproducts of swine.

Pesticides

- **In 1989, household ant killers containing sodium arsenate were banned because of danger of ingestion by small children.**

In 1989, EPA began to phase out household ant poisons containing sodium arsenate because of the danger of ingestion by small children. The EPA Office of Pesticide Programs (OPP) has restricted the use of inorganic arsenic to pressure-treating wood. It has proposed cancellation of all registered uses of inorganic arsenic for nonwood preservative purposes except for the use of calcium arsenate as a turf herbicide, lead arsenate as a grapefruit growth regulator, sodium arsenite as a grape fungicide, and arsenic acid as a crop desiccant, all of which are under review.

Challenge

(11) Would it be important to notify authorities of the patient described in the case? Why?

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Answers to Pretest and Challenge Questions

(1) The patient's drinking water, obtained from an artesian well, may contain elevated levels of arsenic due to leaching from natural mineral deposits in the surrounding bedrock. This phenomenon has been noted sporadically throughout the United States, including the Northwest. The patient's employment in carpentry and home construction may place him in contact with arsenic-containing wood preservatives used to treat lumber. Exposure may potentially occur percutaneously in the course of repeatedly handling moist, freshly treated lumber or via inhalation or ingestion of wood dust liberated during sawing. Ingestion or inhalation of ash or flue gas created during burning of arsenic-treated wood in his home fireplace or wood stove may also be a source of household arsenic exposure.

(2) A sample of the patient's well water can be sent for arsenic analysis. Lists of qualified laboratories may be obtained from the county or state health department. The patient should be questioned about his use of arsenic-treated wood and wood preservatives: arsenic content may be listed on product containers or on Material Safety Data Sheets available from the supplier. The supplier should also indicate whether purchased lumber has been treated with arsenical wood preservatives. The patient should be questioned regarding possible use of arsenic-containing pesticides. In any case of suspected arsenic intoxication, the physician should consider the possibility of intentional poisoning and notify social agencies, if appropriate.

(3) Because nontoxic trimethylated organic arsenic (arsenobetaine or arsenocholine) ingested in a seafood meal may markedly elevate *total* arsenic levels, the patient should be questioned about ingestion of seafood within the past 2 days. If seafood has been ingested, laboratory speciation of the urinary arsenic can eliminate the contribution of arsenobetaine or arsenocholine. However, given the patient's clinical presentation, exposure to toxic inorganic arsenic is likely.

In this case, speciation reveals inorganic arsenic present at 1700 µg/L, monomethyl arsonic acid at 2200 µg/L, and dimethyl arsenic acid at 2100 µg/L, confirming that the patient has sustained inorganic arsenic exposure. Since most laboratories do not provide speciation, an alternative approach to interpreting a high urinary arsenic concentration (>500 to 1000 µg/L) if seafood ingestion is a possible factor would be to repeat the measurement with a new urine sample 48 to 96 hours after complete avoidance of seafood. The trimethylated fish arsenic should be completely cleared by that time, but the metabolites of inorganic arsenic, which have slower clearance, should still be present at elevated levels.

(4) The patient's problem list includes peripheral neuropathy, hyperpigmentation and hyperkeratotic skin lesions, macrocytic anemia, and liver transaminase elevation. The neurologic, dermatologic, and hematologic abnormalities are highly suggestive of chronic arsenic intoxication. He has a characteristic stocking-glove peripheral neuropathy, with predominantly painful sensory symptoms, in the absence of apparent cranial nerve or central nervous system dysfunction. His skin displays hyperpigmentation and palmar-plantar hyperkeratoses characteristic of chronic arsenic ingestion. Consistent laboratory findings include a CBC and peripheral blood smear displaying macrocytic anemia, relative eosinophilia, and occasional basophilic stippling, and a chemistry panel revealing slight elevation in liver transaminases.

(5) Guillain-Barré syndrome is a primarily motor neuropathy that may begin shortly after a viral infection or immunization. Although the patient's neurological complaints began 1 month after a flu-like illness, examination failed to reveal the characteristic rapid tempo and motor predominance of Guillain-Barré syndrome. Chronic alcoholism may be associated with sensorimotor peripheral neuropathy, macrocytic anemia, and liver transaminase elevation, but cerebellar ataxia and other findings such as hepatomegaly and telangiectasia are usually also present with alcoholism. Thallium intoxication may also result in a sensorimotor peripheral neuropathy. Other diagnostic considerations include paraneoplastic syndromes, particularly those associated with lung cancer, diabetes mellitus, and certain chronic inflammatory neuropathies.

(6) The patient's urine should be screened for the presence of arsenic and thallium using either a 24-hour urine collection or a first void morning specimen. A chest X ray should be examined for occult malignancy. Referral for electromyography and nerve conduction studies may be useful to further characterize the peripheral neuropathy and to establish an objective baseline for follow-up measurement. Dermatologic assessment of the patient's skin lesions, possibly including skin biopsy, is indicated to evaluate for cancer or to characterize a precancerous state. The possibility of diabetes mellitus can be investigated by measuring a fasting blood glucose.

(7) Arsenic-induced skin changes generally result from chronic arsenic exposure and have a latency of several years. Hyperpigmentation typically precedes hyperkeratoses, which in turn precede dermal neoplasms. The presence of both hyperpigmentation and palmar-plantar keratoses in the patient suggests that his arsenic exposure began at least 3 years ago, before consumption of drinking water from his current well. Since he resided on nearby property for 10 years, the well at that location should also be suspected of containing high levels of arsenic.

(8) The patient's wife, who resides with the patient and may consume the same well water, is at risk for chronic arsenic poisoning. Residents in the surrounding geographical area, who may also be obtaining water from artesian wells should be considered at risk. Former area residents who consumed arsenic chronically before moving away constitute a third group potentially at risk for delayed development of arsenic-associated disease.

(9) A careful history reveals that the wife, unlike the patient, consumed the well water infrequently, preferring instead to drink bottled soft drinks and juices. Before moving with her husband 10 months ago, she resided in a metropolitan area geographically remote from the present site, where the water was not obtained from wells. Thus, because her arsenic ingestion was markedly lower and of shorter duration than her husband's, she has not yet developed signs or symptoms of chronic arsenic intoxication.

Both the patient and his wife use the arsenic-containing well water for showers and baths. The substantial amount of arsenic in the wife's hair likely reflects external contamination from this source. The arsenic content of the husband's hair is elevated from a combination of external contamination and internal incorporation into the growing hair. The relative contribution from endogenous and exogenous sources cannot be distinguished through bulk hair analysis.

(10) Immediate cessation of consumption of arsenic-containing well water is the essential first step. Because the utility of chelating agents in reversing or improving the patient's arsenic-related peripheral neuropathy, anemia, and palmar-plantar keratoses is unestablished, chelation treatment cannot be routinely recommended. Analgesics and/or certain tricyclic antidepressants have been reported to be beneficial for the painful dysesthesias associated with peripheral neuropathies. Because some reports indicate that vitamin A analogs (retinoids) may be valuable in the treatment of precancerous arsenical keratoses, referral to a dermatologist for consideration of this treatment is indicated. The patient will remain at risk for the delayed appearance of arsenic-related skin cancer and merits regular, long-term dermatologic follow-up.

(11) Because of the likelihood that other wells in the area contain elevated levels of arsenic, public health intervention may be necessary to prevent other cases of hazardous arsenic exposure.

Sources of Information

More information on the adverse effects of arsenic and the treatment and managment of arsenic-exposed persons can be obtained from ATSDR, your state and local health departments, poison control centers, and university medical centers. *Case Studies in Environmental Medicine: Arsenic Toxicity* is one of a series. To obtain other publications in this series, please use the order form on the inside back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of the Director, at (404) 639-6204.

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Brief Reports

Seasonal Arsenic Exposure From Burning Chromium-Copper-Arsenate–Treated Wood

Henry A. Peters, MD; William A. Croft, DVM, PhD; Edwin A. Woolson, PhD;
Barbara A. Darcey; Margaret A. Olson

• All eight members of a rural Wisconsin family experienced recurring neurological and medical illness over three years, especially during the winter months. Arsenic, in concentrations of 12 to 87 ppm, was noted in the hair of the mother and father, and analysis of hair and fingernails of all family members demonstrated pathological levels of arsenic. For four years the five-room home had been heated with a small wood stove in which outdoor or marine plywood and wood remnants had been preferentially burned. Stove ashes that contained more than 1,000 ppm of arsenic contaminated the living area, and the ratio of copper, chromium, and arsenic pentoxide in this ash matched the ratio used in the chromium-copper-arsenate–treated wood.

(*JAMA* 1984;251:2393-2396)

WOOD IS the major construction material used in the United States, but is susceptible to rapid attack by insects, fungi, and other microorganisms. Treatment of wood with pentachlorophenol, inorganic arsenicals, or creosote preservatives extends its utility and useful life. The burning of chromium-copper-arsenate (CCA) preservative-impregnated wood was associated with a family's many health problems. High arsenic content was noted on hair and nail analysis.

History

A rural family living in northern Wisconsin included the parents, two boys, and four girls ranging from 1 to 30 years old. For three years the parents and children experienced various health problems including sensory hyperesthesias, muscle cramps, recurrent pruritic conjunctivitis, earaches and otitis media, sinusitis, bronchitis, and pneumonitis. A 4-week-old premature neonate was diagnosed as having viral pneumonia and because of recurring respiratory exacerbations was treated with a permanent tracheotomy. The children displayed recurrent "measleslike" rashes consisting of pinpoint hyperemic pruritic dermatitis. The children, who went barefoot, experienced reddened thickened skin on the soles of the feet, and in babies, who crawled on the floor, a rash on the legs, diaper and stomach area, hands, arms, and face developed, which later became desquamated. The youngest member of the family experienced a thrombosed penile artery. All family members complained of malaise, easy fatigue, and a "loose feeling" (lack of sensation) in the arms, hands, feet, and legs. Muscle cramps occurred during the evening hours, often causing the children to awaken the parents from sleep.

By the spring of 1982, headaches were frequent, and the parents complained of "blacking out" for periods of up to two hours followed by feelings of disorientation. The two youngest children had multiple seizures described as grand mal from birth to 1 year. All members experienced frequent nosebleeds and easy bruising. One child was diagnosed by a local physician as having idiopathic thrombocytopenic purpura. The mother's fifth pregnancy resulted in a premature birth diagnosed as placenta previa or abruptio placenta. Most striking was recurring seasonal alopecia, ranging from thinning of hair in the parents to complete baldness in the youngest children. The alopecia was most prominent during the months of March and April, and there was considerable hair regrowth by November and December, after which the cycle would repeat itself (Table 1). All symptoms alleviated during summer months and each year seemed progressively worse in terms of the symptomatology. During the last year the father was unemployed, although he had previously worked in construction and bridge repair. The mother worked as a waitress.

Concerned that the house was the source of the family's health problems, an environmental health group had analyzed blood and urine specimens of family members for carbon monoxide, nitrates, nitrites, thallium, arsenic, calcium, copper, iron, lead, mercury, and zinc, but all results were reported normal. Air analysis of the home by the State Board of Health for carbon monoxide and formaldehyde was within acceptable limits. Concern that the fish in the area might contain heavy metals caused by acid rain, the family had stopped eating fish. Well-water analysis by the State Department of Hygiene was normal for heavy metals, organic compounds, nitrates, nitrites, and radioactivity.

Physical Examination of the Family

The father was admitted to University Hospital, Madison, in June 1982.

From the Department of Neurology, Center for Health Sciences (Dr Peters and Mss Darcey and Olson), and the Department of Environmental Toxicology (Dr Croft), University of Wisconsin, Madison, and the Agricultural Environmental Quality Institute, US Department of Agriculture, Beltsville, Md (Dr Woolson).

Reprint requests to Department of Neurology, University Hospital and Clinics, Center for Health Sciences, University of Wisconsin, 600 Highland Ave, Madison, WI 53792 (Dr Peters).

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Table 1.—Summary of Family Health Condition During the Last Three Years

Family Member No.	1	2	3	4	5	6	7	8
Age, yr	1	2.5	5.5	7	8	9.5	30	30
Sex	M	F	F	F	F	M	F	M
Eye irritations	+	+	+	+	+	+	+	+
[illegible]	+	+	+	+	+	+	+	+
Headaches	+	+	+	+	+	+	+	+
Numbness and tingling	+	+	–	–	–	–	+	+
Nosebleeds	+	+	+	+	+	+	+	+
Alopecia	+	+	+	+	+	+	+	+
Diarrhea	+	+	+	+	+	+	+	+
Dermatitis	+	+	+	+	+	+	+	+
Other diagnoses								
Thrombosed penile artery	+							
Severe viral pneumonia		+						
ITP asthma*					+			
Scarlet fever						+		
Placenta previa, placenta abruptio							+	
Sinusitis and severe hepatitis								+

*ITP indicates idiopathic thrombocytopenic purpura

Table 2.—Analysis of Hair and Fingernails Taken From Family Members at Initial Visit at Clinic for Arsenic Determination*

Family Member	Age, yr	Hair Arsenic, ppm	Fingernail Arsenic, ppm
1	30	87.0† 0.73-2.5	2,988
2	30		
Brushings‡		17.4	1,452
Proximal cut (12 cm)		12.16	. . .
Middle cut (12 cm)		1.59	. . .
Distal cut (12 cm)		0.49	. . .
3	9.5	0.3	
4	8	0.6-4.7	106
5	7	0.39-1.2	1,731
6	5.5	0.17-2.2	1,000
7	2.5	. . .	434
8	1	. . .	8,066

*Normal values for hair, less than 0.65 ppm; fingernails, 0.9 to 1.8 ppm.
†Unwashed hair.
‡Removed from hairbrush.

Somewhat anxious, he admitted to drinking more beer than he should. Physical and neurological examination findings were normal except for congenital clubbing of the fingers and toes. Nerve conduction studies and electromyography (EMG) were normal. Urine zinc excretion of 2.4 mg/L was slightly elevated, with normal levels of copper, lead, and arsenic excretion. Urine thallium levels, done elsewhere, had been reported as normal and were not repeated. Because the alopecia could not be attributed to thallium intoxication, hair samples were analyzed for arsenic, which can also produce hair loss.[1] The hair was found to contain 87 ppm (normal, 0.65 ppm).[2] Arsenic levels were determined by atomic-absorption spectroscopy after acid digestion.[3]

Urine, fingernail, and multiple hair samples were collected from the mother and children and analyzed for arsenic. Although no arsenic was detected in the urine, extremely high concentrations were found in the fingernails. Some of the hair arsenic levels were also elevated. Ranges are reported in Table 2. The administration of penicillamine (250 mg three times daily for one week) to the father and one child failed to produce notable urinary excretion. Clinically, we were unable to detect Mees' lines[4] (characteristic of acute extreme arsenic exposure) in the fingernails or toenails of the parents or children. Minimal hyperkeratosis was noted on the palm's surface of the three youngest children. Despite subjective complaints of numbness and tingling, no sensory shading or other sensory abnormality was evident on neurological examination. Family pictures confirmed the history of severe alopecia in the children. The hair loss, although less severe, was still present during the summer.

Home Visit

Foul play was initially suspected, but because both parents were clinically involved, the likelihood of intentional poisoning was lessened.

The family lived in a three-bedroom ranch-style house that had been enlarged room by room from a small cabin as the family grew. Multiple food samples, paint, broiler grease, dust from wall heaters, and ash from a wood-burning kitchen stove (the principal source of heat) were collected and analyzed for arsenic. In addition, air samples were taken to be analyzed for arsenic. The food samples contained insignificant quantities of arsenic. The air sample contained 0.300 μg of arsenic per cubic meter of air and 0.040 μg of arsenic per cubic meter of air for the background sample. The ashes from the stove and chimney area contained arsenic in excess of 1,000 ppm. Specimens of dust and ash collected from around the stove area contained arsenic at 100 to 600 ppm.

The high arsenic content in the ash from the stove covering parts of the floor suggested this as a probable source of poisoning. After the analyses were complete, the father reported that for four years he had been burning large amounts of plywood remnants in the kitchen stove. These wood scraps were made available to him from a construction site where he had worked. Much of the plywood had been CCA treated with a solution of 47% chromium oxide, 19% copper oxide, and 34% arsenic pentoxide. The CCA solution was factory applied at a rate of 4.0 to 6.4 kg/cu m of wood.[5] The proportions of these metals in the ash were the same as in the treatment solution (2.2:1:1.8).[3] The small wood stove located in the kitchen-dining area was loaded from the top. Adding plywood and wood scraps would allow the escape of ashes and

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volatilized fumes from the stove. The father would at times remove the stovepipe from the chimney during the winter and carry it through the dining room and hallway outdoors where the flue ash was removed. Usually the stove continued to burn while this maneuver took place. Soot and ashes were prominent in the kitchen, especially on the floor. Because this was the warmest room in the house, the smallest children played in it and the mother also spent most of her time there.

Since June of 1982 when the diagnosis of arsenic poisoning was made, the family has stopped burning the CCA-treated wood, and cleanup operations were made of the home along with attempts to resettle the family in a noncontaminated environment. Because of lack of funds, the family has been unable to relocate, and current efforts are directed at additional cleaning of the house itself, in which the walls and even the soil around the cabin showed arsenic content. The fourth youngster who had a tracheostomy and slept under oxygen at night has had the tracheostomy closed. The dermatologic, respiratory, neurological, and other problems have lessened considerably. Close monitoring of this family's health problems will continue.

Comment

An eight-member family from northern Wisconsin experienced health problems involving the eyes, respiratory system, CNS, gastrointestinal (GI) tract, blood, reproductive system, skin, and hair. The exposure to arsenic, copper, and chromium occurred through ingestion, inhalation, and direct contact. This resulted in chronic exposure (1) to the skin and eyes where it caused a pruritic dermatitis; (2) to the respiratory system where it caused severe irritation and some pneumonic problems (almost fatal to the fourth child); (3) to the GI tract where it caused severe diarrhea; (4) to the CNS where it caused loss of sensation, seizures, blackouts, and headaches; and the most puzzling lesions of all, (5) the seasonal hair loss among all the family members. The youngest members of the family experienced the greatest health problems probably because they were crawling on the floor where the ash had accumulated. The reddened soles of the feet and thickened skin of the palms can be explained by exposure to arsenic[8] in the ash. It is interesting to note that the two youngest children experienced seizures primarily between the ages of 4 months to 1 year, when they were constantly crawling in the kitchen-dining area. Note that the fingernails contained up to 5,066 ppm of arsenic (Table 2). Unfortunately, detailed EEG studies were not possible.

The exact amount of arsenic, chromium, and copper to which each family member was exposed could not be determined. Only in acute poisoning can arsenic be detected in both blood and urine. Because no arsenic was detected in the urine of family members even after the administration of penicillamine to two members during the summer, we conclude that their exposure was not recent and hope that the body burden is not excessive. Arsenic reacts with protein sulfhydryl groups and any excess leaves the body. Hair and fingernails are the accepted choice for the determination of chronic arsenic exposure.[1,7,12] Levels detected in the hair of the family members indicated the exposure to, but not the exact dose of, arsenic. Mees' lines were not clinically evident when the father was first studied in June 1982. This was because the exposure was chronic and uniform, and not acute and intermittent, or less likely, because Mees' lines had grown out and were clipped off before we saw the family. Also, the penta form of arsenic is less likely to produce Mees' lines and also does not produce the melanotic darkening of the skin or the hyperkeratosis that is commonly produced by the more toxic or lethal trioxide form of arsenic.

The signs and symptoms of chronic low-level exposure to inorganic arsenic in humans have been described,[1,8,11] and arsenic oxide or pentavalent arsenic induces symptoms and signs similar to those experienced by this family.[1,7,13,16] In the commercial process of making outdoor wood and marine plywood, arsenic pentoxide (combined with chromium and copper solution) was used to treat the wood scraps burned by this family. The temperature of wood burning (far less than in smelting) did not change the form of arsenic V oxide, because arsenic was present in the ash as arsenate. Ginsburg[14] in 1965 reported that arsenic V was absorbed by the proximal renal tubules and excreted in the trioxide form in dogs.[14] However, arsenic trioxide, a potentially more toxic form of arsenic, was not detected in our environmental or biologic samples.[15]

Since in winter the father took the chimney off the still smouldering stove for brief periods several times a month to clean the stack of creosote, carbon monoxide inhalation may also have added to the toxic hazard. We did not see the family during winter, so unfortunately no carbon monoxide air levels could be measured, and the father only removed the chimney when windows and doors to the kitchen were wide open.

The combined effect of arsenic V, chromium, and copper exposure in the human is unknown and needs further study. We were unable to show changes in EMG and nerve conduction studies (on the father). It is possible that the more lethal trioxide form of arsenic would have produced more severe damage to the peripheral nerves. The children, because of the normalcy of their neurological examination results and other practical constraints, were not available for EMG and nerve conduction studies.

The father experienced severe sinusitis of the maxillary sinus and had recent surgery to reopen fused bones in this area. Nasal septum ulcerations have been reported in cases of long industrial elemental arsenic exposures.[1] The youngest members of this family demonstrated thickened, reddened, peeling soles. Similar lesions have been described in Taiwanese people living where soil and water were high in arsenic and toxic fluorescent alkaloids.[8] A high incidence of skin cancer was also reported.[8] Although arsenic has been associated with carcinogenesis in humans,[16] no suggestive changes have been detected in this family.

In the past, inorganic arsenicals were used in agriculture as insecticides, soil sterilants, and herbicides.[17] Monitoring by the Food and Drug Administration has indicated that the level of arsenic in US food supplies is low.[18] Most arsenic is found in the meat-fish-poultry diet, with seafood containing the highest levels.

Sources of environmental arsenic include smelters, electric power plants using arsenic-rich coal, and soil and water found in certain parts of the world.[16]

Human poisoning from the burning of CCA-impregnated wood has not been previously reported and represents the probable source of arsenic exposure in this family. Fowler[18] warned in 1977 that the burning of CCA-treated wood should be studied as a potential health hazard. Our studies of the kitchen-living area were done in the summer and disclosed notable contamination with CCA-rich ash. In the winter months while the CCA-treated plywood was being burned, we would have anticipated even greater contamination. With the increased popularity of burning wood for household heating purposes, the environmental health hazard of burning CCA-treated wood needs recognition and evaluation. The role of chromium and copper in contributing to these health problems is conjectural. We would suggest that all three elements could be responsible for this kaleidoscopic clinical pattern.

Joy Savides Felker provided advice and secretarial aid and Lee Sjouik, MS, contributed technical assistance.

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ATSDR June 1990

Case Studies in Environmental Medicine

8

Asbestos Toxicity

Environmental ALERT . . .

- ☑ ***Although asbestos has been banned from use in many products, it will remain a public health concern well into the 21st century.***
- ☑ ***Intact asbestos sources in the home release few fibers and should be left undisturbed. Damaged or crumby materials should be repaired or removed only after receiving professional advice.***
- ☑ ***Asbestos exposure is associated with asbestosis, mesothelioma, and lung cancer, and may cause cancer at extrathoracic sites.***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. The Agency for Toxic Substances and Disease Registry (ATSDR) and the Centers for Disease Control (CDC) designate this continuing medical education activity for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association and 0.1 continuing education units for other health professionals. See pages 21 to 23 for further information.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

A 10-year-old boy with shortness of breath and recent asbestos exposure

A 10-year-old boy is seen at your office with a chief complaint of shortness of breath. Exertional dyspnea has been present for the previous month and is associated with intermittent dry cough. The patient has no associated fever, chills, or chest pain. Chart review indicates no history of asthma or other pulmonary disease, although the patient has been seen several times for "hay fever."

The patient is accompanied by his mother, who appears quite anxious. The mother emotionally relates that her 65-year-old cousin has recently been diagnosed with mesothelioma and is dying. Furthermore, he had been a custodian at the patient's school for the previous 3 years, after retiring from his career as a longshoreman. His work at the school involved general cleanup and boiler room maintenance. The mother is afraid that her son's dyspnea and cough are related to asbestos exposure at the school and that he may be developing mesothelioma since he often helped his cousin after school. Recent asbestos removal in the school has increased the mother's concern.

On physical examination, the patient is in no acute distress. Respirations are unlabored. Lung auscultation reveals a diffuse, expiratory wheeze. Spirometry performed in the office shows an FVC of 95% of predicted value and an FEV_1 of 88% of predicted value with an FEV_1/FVC of 70%. The remainder of the examination is within normal limits. A chest X ray is normal.

Pretest

(a) Discuss whether the patient's symptoms are related to asbestos exposure.

(b) Is the patient at risk for future disease? Explain.

(c) Can the cousin's mesothelioma be related to his work as a custodian in the school? Explain.

Answers to the Pretest can be found on page 19.

Exposure Pathways

☐ **Asbestos exposure occurs primarily through inhalation of fibrous dust.**

☐ **Insulating materials produced prior to 1975 commonly contain asbestos.**

Asbestos is a generic term for a group of six naturally occurring fibrous minerals. The basic unit of asbestos-class minerals is the silicate combined in varying proportions with magnesium, iron, calcium, aluminum, and sodium or trace elements.

There are two major classes of asbestos: serpentine, which contains a magnesium silicate called chrysotile, and amphiboles, which represent a small portion of the world's asbestos consumption and include crocidolite, amosite, anthophyllite, and tremolite. Chrysotile, the sole member of the serpentine group, accounts for 93% of the world's asbestos use.

Asbestos has been used in over 3000 products due to its high tensile strength, relative resistance to acid and temperature, and its varying textures and degrees of flexibility. It does not evaporate, dissolve, burn, or undergo significant reactions with other chemicals, which makes asbestos nonbiodegradable and environmentally cumulative.

Although many applications have been phased out of production, uses of asbestos have included the following:

Commercial

Boilers and heating vessels
Cement pipe
Clutch, brake, transmission components
Conduits for electrical wire
Corrosive chemical containers
Electric motor components
Heat protective pads
Laboratory furniture
Paper products
Pipe covering
Roofing products
Sealants and coatings
Textiles (including curtains)

Homes and Buildings

Duct insulation
Fire protection panels
Fireplace artificial logs or ashes
Furnace insulating pads
Fusebox liners
Heater register tape and insulation
Joint compounds
Patching plaster
Pipe or boiler insulation
Sheet vinyl or floor tiles
Shingles
Textured acoustical ceiling
Underlayment for sheet flooring

Asbestos fibers may result from mining, milling, and weathering of asbestos-bearing rock, and from the manufacture, wear, and disposal of asbestos-containing products. Because of the widespread use of asbestos, its fibers are ubiquitous in the environment.

Although bans and voluntary phaseouts have contributed to declining production of asbestos since the early 1970s, it is still used in construction materials, mostly asbestos cement products. Building insulation materials manufactured since 1975 may no longer contain asbestos; however, products made or stockpiled before the ban remain in many homes.

Indoor air may become contaminated with fibers released from building materials, especially if they are damaged or crumbling. Common sources in homes are sprayed asbestos ("cottage cheese") ceilings, pipe insulation, boiler coverings, wallboard, and floor and ceiling tiles. Homeowners should not undertake repair or removal of asbestos-containing materials without professional guidance or services.

Although measurable asbestos levels in schools are usually 1000 times below the permissible exposure limit (PEL) for work environments, public concern has led to widespread removal and abatement programs. However, some facilities have higher levels of airborne asbestos after removal than before, indicating that removing asbestos improperly can be more hazardous than leaving it in place.

Street dust may contain fibers from brake linings or crushed asbestos-containing rock used in road construction. Fibrous tremolite, the asbestos commonly found in talc, has also been found in play sand.

Drinking water supplies may become contaminated with asbestos from erosion of natural land sources, discarded mine and mill tailings, asbestos cement pipe, and from disintegration of other asbestos-containing materials transported via rain. Most water supply concentrations are less than 1 million fibers per liter but in some cases have exceeded 100 million fibers per liter. The U.S. Environmental Protection Agency's (EPA) proposed maximum contaminant level for asbestos in drinking water is 7 million fibers (larger than 10 microns in length) per liter.

Challenge

(1) *Additional information for the case study: The patient and his family live in a home built in 1955. Pipes in the basement are covered with asbestos insulation. Should the family consider the removal of all asbestos pipe coverings in their home? Explain.*

ATSDR

Who's at Risk

- **The construction trades have the most heavily asbestos-exposed workers.**
- **Spouses and family members can be exposed through asbestos dust on worker's skin and work clothing.**
- **Cigarette smoke increases the risk of asbestos-associated lung cancer.**

In the past, asbestos exposure was associated mainly with mining and milling of the raw material and with workers engaged in product manufacture. Since industrial use has decreased over the last 40 years, these occupational exposures have declined. Today, most exposures occur during repair, renovation, removal, and maintenance of asbestos that was installed years ago. The number of new exposures to the general population from in-place asbestos, however, may be greater in number than the exposures to all earlier workers combined.

The most heavily exposed people in the United States are construction tradespersons. In 1988, there were 6,300,000 active construction workers in the United States. Since most asbestos has been used in construction, and two thirds of today's production is still used in this trade, risk to these workers may be considerable. Carpenters, utility workers, electricians, pipefitters, steel mill workers, sheet metal workers, boilermakers, and laborers are at risk of exposure to asbestos through construction materials, insulation coverings of pipes, boilers, industrial furnaces, and other sources. Mechanics working with brake and transmission products also may be exposed to asbestos.

Secondary exposure occurs when fibers released to the air are inhaled by persons not directly handling asbestos. For example, 4 to 5 million shipyard workers were exposed when a relatively small number of insulation workers applied asbestos to ships' pipes and hulls. Domestic and environmental asbestos exposures may also occur indirectly. Asbestos-related diseases have occurred in family members whose only contact was dust from an exposed worker's clothes. Similar diseases were also found in persons who grew up within one-half mile of an asbestos factory.

Cigarette smoking and exposure to other carcinogens greatly increase the risk of asbestos-associated lung cancer. A comparison of the experiences of 17,800 asbestos insulation workers with matched controls showed that asbestos workers who did not smoke suffered 5 times the number of lung cancer deaths than controls who neither smoked nor worked with asbestos (55 deaths per 100,000 man-years for asbestos workers who did not smoke compared with 11 deaths per 100,000 man-years for controls who were neither asbestos workers nor smokers). Persons who smoked but did not work with asbestos had a death rate of

122 per 100,000 man-years; and among persons with both exposures (asbestos and cigarette smoking), 601 deaths occurred per 100,000 man-years. There is evidence that cigarette smoking in asbestos workers is also associated with increased risk of cancer of the esophagus, oropharynx and buccal cavity, and larynx. Cancers of the stomach, colon-rectum, and kidney, however, do not appear to be synergistically affected by smoking and asbestos exposure since smoking and nonsmoking asbestos workers suffer equal incidences of these health effects. While cancer, when established, may be irreversible, cancer risk is reversible. Data indicate that risk diminishes when smoking ceases.

Challenge

(2) On questioning the mother, you learn that the father of the boy described in the case study is a master carpenter who specializes in restoring Victorian-style homes. What are the potential sources of asbestos exposure for the child?

(3) The spouse of the mother's cousin is reportedly in good health. Should she be screened for asbestos-related disease? Explain.

Biologic Fate

- ☐ **A significant proportion of inhaled asbestos fibers may be retained in the lungs.**
- ☐ **The size and shape of asbestos fibers affect the lungs' ability to effectively remove them.**

The primary route of asbestos entry into the body is through inhalation. Ingestion of asbestos fibers can occur from drinking contaminated water or after mucociliary clearance from the lungs. The fate of ingested asbestos is still being debated. Asbestos fibers may also lodge in the skin.

Generally, only particles between 0.5 and 5 microns in diameter with a length-to-width ratio of 3:1 will be deposited in the respiratory regions of the lung (alveoli and terminal bronchioles). Larger particles tend to be filtered out in the upper airway and nasopharynx. Smaller fibers tend to remain suspended in the inspired air, and the majority are exhaled. However, asbestos is an exceptional substance: fibers ranging from 5 to 10 microns in diameter can also penetrate to the lower respiratory regions of the lung, where they may have destructive effects.

The fibrous nature of asbestos renders the lungs' defense mechanisms ineffective. Smaller, nonfibrous particles are normally engulfed by macrophages and removed by lymphatic or mucociliary mechanisms. Attempts by the macrophages to engulf fibers can lead to eventual deposition in various tissues of ferrous material in a drumstick configuration called a ferruginous body (asbestos body).

Asbestos fibers can also penetrate to the terminal bronchiolar level and enter the peribronchiolar space, resulting in a fibrogenic response. Because the fibers concentrate in the lower lung fields, there is a tendency for fibrosis to occur first in the lungs' bases, and for pleural effects to be confined to the lower two-thirds of the thorax. Fibrosis results from persistent release of inflammatory mediators such as lysozymes, interleukins, and fibroblast growth factors at the site of asbestos fiber penetration and deposition.

Data do not clearly relate GI tumors or peritoneal mesotheliomas to direct ingestion of asbestos fibers, although persons exposed to asbestos by inhalation have been reported to have a twofold greater risk of colorectal cancer than unexposed persons. Some investigators believe this malignancy is caused by fibers removed from the lungs' upper respiratory regions by ciliary mechanisms and then swallowed. Most reports suggest that ingested asbestos is excreted with the feces. Asbestos bodies have been identified within some human specimens of colorectal adenocarcinomas. Several animal studies have revealed that asbestos fibers are capable of penetrating the GI tract.

Electron microscopy reveals that fibrils result from longitudinal and cross-sectional fragmentation of asbestos fibers. A single asbestos fiber can fracture into hundreds of sub-microscopic fibrils. Research indicates that these uncoated fibrils may be the form that migrates into the peritoneal and pleural spaces.

Physiologic Effects

The respiratory, immunologic, cardiovascular, and gastrointestinal systems may be adversely affected by asbestos inhalation and by ingestion subsequent to mucociliary removal from the respiratory tract. Skin nodules from handling asbestos-containing materials may also occur.

☐ **Asbestos primarily affects the respiratory system. The immune and cardiovascular systems, and possibly the GI system, are also affected by asbestos exposure.**

Immunologic abnormalities such as increased concentrations of auto-antibodies and depressed lymphocyte responsiveness (page 10) are usually mild or absent in persons who have not developed clinical signs of asbestosis. Cardiovascular effects are secondary to pulmonary changes. Fibrosis in the lung can lead to increased resistance to blood flow through the pulmonary capillary bed, resulting in pulmonary hypertension and compensatory hypertrophy of the right heart.

No deaths due to acute exposure to asbestos have been reported. However, delayed death due to asbestosis and cancer from chronic inhalation exposure has occurred. The risk of developing asbestos-associated disease continues even after exposure has ceased.

Respiratory Effects

Inhalation of asbestos fibers may cause parenchymal and pleural asbestosis, mesothelioma, and carcinoma. All four syndromes can be present in a patient. Exposure to other carcinogens, dose and duration of exposure, individual susceptibility, and elapsed time since initial exposure all may play a role in disease development. Chronic low-level asbestos exposure has been associated with lung cancer, mesothelioma, and pleural diseases, including pleural asbestosis; higher doses are more likely to produce parenchymal asbestosis. Smoking and exposure to other toxins increase the risk of asbestos-associated lung cancer.

☐ **Asbestos exposure may result in asbestosis, mesothelioma, or carcinoma.**

Asbestosis

☐ **Asbestosis is pulmonary interstitial fibrosis of the pleural or parenchymal tissue.**

☐ **Pleural plaques have not been shown to be premalignant.**

Inhalation of asbestos fibers can lead to a characteristic pneumoconiosis, or diffuse interstitial fibrosis, termed asbestosis. Either heavy exposure for a short time or lower-level exposure over a longer period may result in asbestosis; cases have resulted from intense exposure of 1 day's duration. The disease can affect the lung parenchyma or pleural tissue. Clinical manifestations typically appear 20 to 40 years after onset of exposure. Radiologic changes can occur before 20 years, however.

Asbestosis patients typically have elevated levels of antinuclear antibody and rheumatoid factors and a progressive decrease in total lymphocyte count with advancing fibrosis. Self-perpetuating host responses may be affecting the progression of fibrosis even after exposure ceases.

Pleural effects can occur even in the absence of parenchymal asbestosis. The incidence of pleural abnormalities in persons employed in asbestos-related occupations can be high (20% to 60%). Asbestos effects on the pleura include plaques (with and without calcification), diffuse pleural thickening, and effusions. Pleural plaques are oval areas of acellular collagen deposits, usually located bilaterally on the inferior and posterior surfaces of the pleura. People in contact with work clothes of asbestos workers or with asbestos-containing household products have developed pleural abnormalities. An asbestosis prevalence of 11% in wives, 8% in sons, and 2% in daughters was reported in families of asbestos-exposed shipyard workers.

Pleural plaques are not lung cancer precursors, although persons with pleural plaques have an increased incidence of lung cancer. Migration of inhaled asbestos to the pleura is the most likely cause of plaques. Pleural thickening can lead to decreased ventilatory capacity, probably because of restrictive effects. These effects are most commonly seen with extensive involvement of the visceral pleura, which is observed radiologically as diffuse pleural thickening.

Mesothelioma

☐ **Mesothelioma is a signal tumor for asbestos exposure and can appear after relatively low-level exposures.**

Mesotheliomas are tumors arising from the thin membranes that surround internal organs. Pleural and peritoneal mesotheliomas are rare in the general, unexposed population and are indicators of asbestos exposure. Although all asbestos types can cause mesothelioma, several studies have suggested that, in humans, the amphibole mineral form may be more likely to induce mesothelioma than the serpentine form.

The dose appears to be lower for asbestos-induced mesothelioma than for pulmonary asbestosis or lung cancer. An extremely short exposure period may be sufficient to cause this rare tumor. However, there is typically a long latency period. Latency periods have been up to 57 years, although more intense exposures can result in latencies as short as 20 to 30 years. Some studies have indicated that risk of mesothelioma from a given level of asbestos exposure depends primarily on the elapsed time since exposure, with risk increasing dramatically after a lag period of about 10 years.

An estimated 1500 cases of mesothelioma per year occur in the United States (compared to an average of 130,000 cases of lung cancer per year, mostly due to smoking). Data on death rates from pleural or peritoneal mesotheliomas over the past 10 to 20 years indicate that mesotheliomas are increasing in males over 65 years of age who have an occupational history of asbestos exposure. Unlike asbestos-related bronchogenic cancer, mesothelioma risk does not appear to be influenced by smoking.

- ☐ **Unlike bronchogenic cancer, mesothelioma risk is not affected by cigarette smoking.**

Lung Cancer

There is little doubt that all types of asbestos can cause lung cancer. A latency period of 10 to 30 years or more exists between the onset of asbestos exposure and occurrence of the tumor. Whether asbestos exposure will lead to lung cancer depends not only on cumulative exposure, but also on other underlying lung cancer risks.

- ☐ **Latency for lung cancer is 10 to 30 years or more.**
- ☐ **It is unclear whether a threshold asbestos dose exists for lung cancer.**

Lung cancers of most cell types (except alveolar cell) have been associated with asbestos exposure. Adenocarcinoma of the lung occurs more often in asbestos-exposed persons than in nonexposed persons. Asbestos-associated lung cancer tends to occur in the lower lung fields, although not exclusively.

Other Carcinogenic Effects

Some mortality studies of asbestos workers have revealed small increases in the incidence of death from cancer at one or more extrathoracic sites, including the kidneys and gastrointestinal system – notably the esophagus, stomach, colon, and rectum. Presumably these cancers are due to swallowing asbestos fibers. In contrast, other epidemiologic studies have not detected statistically significant associations between asbestos ingestion and extrathoracic cancers. Various researchers and regulatory groups have reviewed the weight of evidence and have not been able to reach a consensus on the effects of ingested asbestos fibers. Whether gastrointestinal neoplasms

- ☐ **Increased incidence of gastrointestinal cancers has been reported among asbestos workers.**
- ☐ **The consequences of ingesting asbestos fibers are controversial.**

may be induced by ingesting asbestos-contaminated drinking water remains unproven. In humans, asbestos bodies have been identified in extrapulmonary tissues including tonsils, thoracic and abdominal lymph nodes, pleura, peritoneum, liver, spleen, kidneys, adrenals, small intestine, pancreas, and bone marrow, as well as the lungs.

Cardiovascular Effects

☐ **Cardiovascular effects are secondary to pulmonary fibrosis.**

Fibrosis of the lung can lead to increased resistance to blood flow through the capillary bed, resulting in cor pulmonale. This condition may also occur with less severe fibrotic disease, especially if chronic obstructive lung disease is simultaneously present, as commonly seen in cigarette-smoking asbestos workers. Pulmonary hypertension may occur before decreased respiratory function is clinically detectable.

Immunologic Effects

☐ **Immunologic abnormalities have been noted in persons with asbestosis.**

Immunologic abnormalities have been observed in asbestos workers with clinical signs of asbestosis and have also been reported in persons environmentally exposed. Despite some variability, most studies indicate that cell-mediated immunity can be depressed in workers who have radiologic evidence of asbestosis. Autoantibodies (rheumatoid factor, antinuclear antibodies) are typically present in these workers. Caplan's syndrome (the coexistence of pneumoconioses with rheumatoid changes) also has been noted in asbestos workers, although it is more common in coal miners and workers with other pneumoconioses. The implications of these immunologic changes are difficult to assess, but they are of special concern because depressed immune function might be a factor in the etiology of asbestos-induced cancer.

Challenge

(4) Is the mesothelioma of the patient's cousin likely to be related to his school custodial work? Explain.

(5) How will you explain the patient's potential health risks to his mother?

Clinical Evaluation

History and Physical Examination

The medical evaluation of workers exposed to asbestos includes a thorough medical and occupational history, physical examination, chest X ray, and pulmonary function tests. The same protocol has been recommended for evaluating an asymptomatic patient with a history of asbestos exposure. Pertinent historical information includes the source, intensity and duration of exposure, time elapsed since first exposure, and work history of household members. Asbestos accumulates in the body, and even relatively minor exposures may be important.

☐ **Dry rales, auscultated in the midaxillary line, are the most common lung findings associated with asbestosis.**

The physical examination should focus primarily on the patient's lungs, and particular attention should be paid to pulmonary auscultation. Fine inspiratory rales in the posterior and posterolateral lung bases, audible on deep inspiration, may be the earliest sign of interstitial fibrosis. Generally, however, a chest X ray is more sensitive.

Examination should also assess stigmata of other diseases that may confound the diagnosis of asbestosis. For instance, rheumatoid arthritis is sometimes associated with interstitial fibrosis. Chest-wall configuration, evidence of thoracic surgery, and cardiac status may also affect the diagnosis.

Signs and Symptoms

Significant clinical syndromes include asbestosis, lung cancer, and mesothelioma.

Asbestosis

The most common finding in asbestos-induced pulmonary disease is pleural thickening, often manifested as discrete pleural plaques. Pleural plaques can be seen as radiologic bilateral images of hyalin scar formation on either the visceral or parietal pleural surfaces. Involvement of the parietal pleura rarely is associated with symptoms. Visceral pleural thickening often involves blunting of the costophrenic angles and extends diffusely up the chest walls. If advanced, visceral pleural thickening can be associated with dyspnea and restrictive changes on pulmonary function tests.

☐ **Progressive dyspnea on exertion is a common symptom of asbestosis.**

A patient with asbestosis commonly develops fatigue, weight loss, and insidious onset of dyspnea on exertion. As the disease progresses, the dyspnea worsens. A dry cough typically occurs, but a productive cough, even in a nonsmoker, is not uncommon. Patients often describe a "tight" feeling in the chest. The interstitial disease is radiographically demonstrated as a reticular fibrosis located predominantly in the lower lung fields. Radiologic evidence is often not present until at least 5 years after exposure.

Fibrosis found symmetrically in the lower aspects of both lungs is typically caused by asbestos. Fibrotic lung disease due to asbestos inhalation is often associated with pleural plaque formation, which eliminates other etiologic possibilities such as drugs, radiation, sarcoidosis, collagen vascular disorders, Goodpasture's syndrome, hemosiderosis, idiopathic pulmonary fibrosis secondary to lung infections, and inhaled silica, coal dust, or organic dusts.

Lung Cancer

☐ **Asbestos-associated lung cancers produce the same symptoms as cancers due to other etiologies.**

Lung cancer caused by asbestos exposure cannot be differentiated from cancer caused by other environmental factors. The differential diagnosis of lung cancer in an asbestos-exposed patient should include other possible etiologies such as exposure to cigarette smoke, arsenic, chloromethyl ethers, chromium, nickel, and ionizing radiation. Clubbing of the distal phalanges or cyanosis of the nail beds may be present.

Mesothelioma

☐ **The latency period for mesothelioma is 20 years or more, but the onset of symptoms is sudden.**

Both pleural and peritoneal mesotheliomas may be seen in asbestos-exposed patients. These tumors are rapidly invasive. Although onset of mesothelioma is not sudden, symptoms of the disease may be. Peritoneal mesotheliomas are more difficult to diagnose by noninvasive means than pleural occurrences. They are frequently detectable as an expanding "doughy" feeling on abdominal palpation. Mesothelioma is seldom associated with etiologies other than asbestos exposure.

Laboratory Tests and Special Procedures

☐ **Chest X ray and pulmonary function tests are important procedures in diagnosing asbestos-associated disease.**

Established tests and procedures helpful in diagnosing asbestos-associated disease include radiographic techniques, pulmonary function tests, and possibly computerized tomography scanning. Neither sputum studies nor blood chemistry studies are useful in diagnosing asbestos-associated disease in the clinical setting.

Radiographic Techniques

The chest X ray is the basic tool for assessing asbestos-associated parenchymal and pleural disease. Radiographic findings may include interstitial fibrosis in the lower lung fields and thickening of both the parietal and visceral lung pleura. Parietal pleural thickening generally appears as a lobulated prominence of the pleura adjacent to the thoracic margin. Visceral pleural thickening is generally more diffuse and appears as interlobar fissure thickening on lateral films. A system has been proposed by the International Labor Organization for radiographic rating of the changes in pneumoconioses. The diagnosis of asbestosis should be made in the context of the overall clinical presentation and should include, but not emphasize, X-ray findings. The association of pleural thickening and calcification enhances diagnostic accuracy; however, open lung biopsy is the only definitive diagnostic test for asbestosis.

- ☐ **Radiographic results should not be used preferentially in diagnosing asbestosis.**

The radiologic appearance of asbestos-induced lung cancer does not differ from that of other cancers. Asbestos-related malignancies predominantly involve the lower portion of the lungs, but they are not restricted to this location.

Computerized Tomography

Computerized tomography (CT) scanning is a particularly sensitive means of differentiating asbestos-related pleural plaques from soft-tissue densities. The technique is being used to diagnose other asbestos-associated abnormalities as well. Because it is considerably more expensive than standard X rays, CT scanning should not be considered a screening tool.

- ☐ **CT scanning is too expensive for use as a screening tool, but may be helpful in certain cases.**

Pulmonary Function Testing

Nonsmoking patients with asbestosis typically have spirometric changes indicative of small airway disease and restrictive defects; smokers with asbestosis may have a combined obstructive/restrictive pattern. Small airway disease is a common early finding and is reflected in a 25% to 74% reduction of forced expiratory flow rates. This change may reflect early fibrosis in the peribronchiolar areas or inflammatory changes. Restrictive defects are observed as a reduction in forced vital capacity. Because such reduction may also occur in obstructive airway disease, an apparent combined pattern of restrictive and obstructive disease should be followed up with further pulmonary studies including carbon monoxide diffusion capacity and static

- ☐ **Small airway disease and restrictive defects are typical in nonsmoking patients with asbestosis; combined obstructive/restrictive pattern is more typical in smokers.**

lung volumes. True restrictive disease generally manifests as a decrease in total lung capacity with normal or residual volume, which can be determined using both the plethysmographic and helium dilution methods.

Sputum Studies

Sputum inspection for asbestos fibers or ferruginous bodies has been advised, but most investigators now agree that the lack of sensitivity and specificity precludes their use for screening purposes. Sputum cytology remains useful as a diagnostic test for neoplasia and lung cancer, however.

☐ **Sputum studies are not useful for screening patients exposed to asbestos.**

Other Tests

Recent studies suggest that lymphocyte abnormalities (particularly T-cell) correlate with both asbestos-related malignancies and asbestosis. However, because these findings are in the early investigative stage, they are not clinically useful. There is no blood test that is useful for diagnosing asbestos-associated diseases.

Challenge

(6) Is the father (aged 50) of the patient described in the case study at risk of asbestos-associated disease; if so, what medical evaluation should be undertaken?

Treatment and Management

Management of asbestos-associated diseases begins with patient education regarding smoking cessation and avoidance of pulmonary infections. Awareness of early symptoms of other neoplasms is important, including hoarseness, sores in the mouth, blood in the urine, blood in the stool, and gastrointestinal symptoms. Persons exposed to asbestos should be advised of the increased risk of lung cancer and the synergistic effects of cigarette smoking, although smoking does not affect the development of mesothelioma. Explaining environmentally related cancer risk is difficult because extrapolation of risk from workplace data is impossible in many cases. Maintaining a balance between appropriate concern and avoidance of undue alarm is the goal.

☐ **Patient education is an important factor in managing asbestos-associated disease.**

Follow-up of asymptomatic patients exposed to asbestos is recommended to facilitate early diagnosis and intervention. Periodic pulmonary function studies can be helpful in diagnosing early signs of asbestosis.

Asbestosis

Asbestosis is an irreversible pulmonary condition. Respiratory infections should be treated aggressively since they often prove fatal in patients with advanced fibrotic lung disease. Patients should be strongly advised to avoid all pulmonary irritants including cigarette smoke. Influenza and pneumococcal vaccines are warranted. In the later stages, pulmonary rehabilitation may be helpful. The patient should be advised to consult a physician when the first signs and symptoms of respiratory infection occur so that early treatment can be instituted.

☐ **Asbestosis patients should avoid pulmonary irritants and guard against lung infections.**

☐ **Most pleural plaques are benign and require no specific treatment.**

Although most investigators consider the pleural plaques associated with asbestosis to be benign, they can result in pulmonary impairment. Patients with pleural asbestosis are also more likely to have or develop parenchymal asbestosis and should be followed appropriately. Patients should be informed that pleural plaques represent evidence of significant asbestos exposure.

Cancer

Mesothelioma

The prognosis for patients with mesothelioma is poor; they seldom live longer than 12 to 18 months after diagnosis. The 1-year survival rate of mesothelioma patients is less than 30%, and no efficacious treatment has been identified. Palliation and support are recommended.

☐ **Patients with mesothelioma have a 1-year survival rate of less than 30%.**

Lung Cancer

☐ **Treatment of asbestos-associated cancer does not differ from treatment for cancers due to other causes.**

Treatment of asbestos-associated cancer should include appropriate combinations of surgery, chemotherapy, and radiation, according to accepted surgical and oncological standards.

Challenge

(7) If examination of the father of the child described in the case study is entirely normal except for bilateral pleural plaques, what follow-up will you recommend?

(8) As a concerned family physician, you become identified as a community resource on asbestos exposure and accept an invitation to speak at a Parent-Teacher Association meeting. What will you tell your audience?

Standards and Regulations

Workplace

In the 1930s, widespread evidence of asbestos-associated disease in workers was found. A standard for exposure was not established in this country until 1960 in selected industries; in 1971, it was extended industrywide. A 1968 British study judged that exposure to 2 fibers per cubic centimeter of air (fibers/cc) for the duration of a person's worklife would result in approximately a 1% risk of developing asbestosis, which was an underestimation. This estimate, nonetheless, led to the 1976 U.S. standard of 2 fibers/cc as a time-weighted average (TWA). Further study of carcinogenicity resulted in the U.S. standard of 0.2 fibers/cc (8-hour TWA), effective in 1986. The current level at which employers must take action to reduce employee exposure (action level) is 0.1 fibers/cc (8-hour TWA).

☐ **The current OSHA standard for asbestos in the workplace is 0.2 fibers/cc of air as an 8-hour TWA.**

Environment

The difficulties of controlling asbestos exposure in the workplace are paralleled in the general environment. EPA recommends "no visible emissions." In 1973, EPA banned spraying of asbestos in building interiors. Currently there is no regulation for asbestos in potable water. EPA's proposed maximum contaminant level (MCL) for asbestos in drinking water is 7 million fibers (larger than 10 microns in length) per liter of water.

☐ **EPA's proposed MCL for asbestos in drinking water is 7 million fibers per liter of water.**

The Asbestos in Schools Identification and Notification Act of 1982 requires that local education agencies 1) inspect for friable material, 2) analyze these materials for asbestos content, 3) post results and notify parents and employees if asbestos is found, and 4) maintain appropriate records. A recent study indicating that power-buffing and power-stripping of asbestos-tile floors in schools produces significant airborne-asbestos levels has prompted an EPA warning to school communities. Floor maintenance will henceforth be performed by hand to prevent the release of fibers.

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Suggested Reading List

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Walker AM. Declining relative risks for lung cancer after cessation of asbestos exposure. J Occup Med 1984;26:422-6.

Government Publications

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Answers to Pretest and Challenge Questions

Pretest

The Pretest can be found on page 1.

(a) The patient's symptoms are unlikely to be related to asbestos exposure. The patient's after-school activity for only 3 years is much less than the typical latency period for asbestos-associated diseases in workers. Asbestos levels measured in the general indoor air in schools also tend to be well below the OSHA permissible workplace level. A more likely cause of the boy's symptoms would be onset of bronchial asthma.

(b) The patient's potential exposure could place him at risk for future asbestos-related complications. Even low-level environmental asbestos exposures can eventually result in disease.

(c) The cousin's mesothelioma is unlikely to be related to his 3-year history of school custodial work. A number of cases of mesothelioma in long-term school custodians have been documented, however. In several recent studies, school custodians were also found to have asbestotic chest X rays. Exposure to airborne asbestos while working as a longshoreman is the more likely cause of the cousin's disease.

Challenge Answers

Challenge questions begin on page 3.

(1) If the pipe coverings are visibly in good condition and air sampling indicates no release of fibers, it is probably safer to leave them intact. Application of a substance to encapsulate the intact asbestos may be considered. If the pipe coverings are deteriorating, however, the family should seek professional advice from a qualified and licensed contractor specializing in asbestos abatement.

(2) The patient may be exposed to low levels of asbestos at home, school, and play. Asbestos materials adequately contained and not airborne are not likely to be a significant hazard, but asbestos does tend to be liberated from aging materials such as wall and ceiling insulation, or pipe and duct coverings. Asbestos-containing materials aggressively abraded may also release fibers. Power-buffing of asbestos-containing floor tiles is an example. The father's occupation suggests the patient could be receiving secondary asbestos exposure from dust brought home on his father's work clothes and person.

(3) Yes, workers exposed to asbestos can bring fibers home on their clothes, skin, and hair, inadvertently exposing others in the household.

(4 See (c) in the Pretest answers above.

(5) For the child described in the case study, the physician should clearly state that the child's symptoms are not likely to be attributable to asbestos, without unduly minimizing the possible long-term risks of asbestosis or cancer. The synergistic effects of smoking and exposure to other carcinogens should be discussed. If either or both parents smoke cigarettes, the child may be more likely to become a smoker himself, and thereby increase his risk of asbestos-related lung cancer. Also, parental smoking could expose the child to "second-hand" smoke.

(6) Yes, the father may be at increased risk for asbestos-related disease. Homes built before 1975 were typically constructed with asbestos-containing products. Removing or repairing these materials could liberate asbestos fibers that might be inhaled if appropriate respiratory protection is not worn.

A thorough medical and occupational history; a physical examination, including auscultation of the heart and lungs; chest X ray; and spirometry to assess possible restrictive and/or obstructive pulmonary disease may be indicated. Stool hemoccult testing is also advised.

(7) It would be prudent to have periodic evaluations including chest X ray and pulmonary function testing, and screening for colorectal cancer on a yearly basis.

(8) Parents often feel resentful that they have not been informed earlier of an asbestos hazard. A respected physician in the community is often able to put the risk of disease due to asbestos into perspective for such an audience. Before making public statements, however, it would be advisable to consult with state and local public health officials on the potential for asbestos exposure in local schools.

Sources of Information

More information on the adverse effects of asbestos and the treatment and management of asbestos-exposed persons can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Asbestos Toxicity* is one of a series. For other publications in this series, please use the order form on the back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of Director, at (404) 639-0730.

ATSDR October 1992

Case Studies in Environmental Medicine

11

Benzene Toxicity

Environmental ALERT . . .

☑ ***Benzene is an important commercial commodity and has become widespread in the environments of developed countries.***

☑ ***In the United States, gasoline contains up to 2% benzene by volume; in other countries, the benzene concentration in gasoline may be as high as 5%.***

☑ ***Benzene in the workplace has been associated with aplastic anemia and leukemia and may also cause nonhematologic cancers.***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. See page 19 for more information about continuing medical education credits and continuing education units.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

A 50-year-old diesel mechanic with recurring nosebleeds, fatigue, and weight loss

A 50-year-old man is prompted to visit your office because of a nosebleed that has been recurring for 2 days. He says that this is the third episode of nosebleeds in the last 6 months. He expresses concern that he becomes easily fatigued at work, and 2 months ago he began noticing bruises on his arms and legs, although he does not recall the causes. He has lost more than 12 pounds in the last 2 years, which he attributes to loss of appetite.

History of previous illness includes a fractured arm in childhood. He has had three bad colds in the past 2 years that lasted for more than a week and included coughing and breathing difficulty. The patient occasionally drinks beer; he quit smoking cigarettes 4 years ago. He does not have allergies and is taking no medications at this time.

On examination, you find a muscular man with somewhat pale and dry skin. Conjunctivae are pale. Numerous ecchymoses and petechiae are noted on arms and legs. Many seem to be old with incomplete healing. BP is 138/84; HR is 94. Temperature is normal. His throat is moderately inflamed, and prominent cervical nodes are palpable. Examination is otherwise within normal limits.

On further questioning, you learn that the patient is a diesel mechanic and has worked on trucks for the same employer for the previous 12 years. He and his wife divorced 8 years ago; his wife became nervous and withdrawn after two miscarriages, which led to marital stress. He has lived in his home for the past 16 years. He has a daughter, age 16, who lives with his ex-wife.

Laboratory studies reveal the following: glucose, BUN, and bilirubin within normal limits; Hgb 10.2 g/dL (normal 14.0-18.0); Hct 32.6% (44.8-52.0); RBC 3.32 mil/mm^3 (4.3-6.0); MCV 98 fl (80-100); MCH 31 pg (26-31); MCHC 31% (31-36); WBC 1500 mm^3 (5000-10,000); segs 60% (40-60); bands 1% (0-5); lymphs 31% (20-40); monos 8% (4-8); platelets 50,000/mm^3 (150,000-400,000). A chest X ray is negative except for some suggestion of hyperlucency; ECG is normal.

Pretest

(a) What is the problem list for this patient? What is the differential diagnosis?

(b) What additional testing would you recommend?

(c) What measures would you take to manage the case and treat this patient?

Answers to the Pretest can be found in Challenge answers (3) through (7) on pages 17 and 18.

Exposure Pathways

- ☐ **Benzene is commonly used as a solvent and as a raw material in chemical syntheses.**
- ☐ **Benzene is added to unleaded motor fuels for its antiknock characteristics.**
- ☐ **Because benzene plays such a vital role in many industrial processes and is a component of gasoline, it is widespread in the environment.**

Benzene (C_6H_6) is the first member of a series of aromatic hydrocarbons recovered from refinery streams during catalytic reformation and other petroleum processes. It is a clear, colorless, highly flammable liquid at room temperature. Its vapor is heavier than air and can travel to a source of ignition and flash back. It has a pleasant odor detectable at concentrations greater than 4 parts per million (ppm). (The workplace permissible exposure level [PEL] is 1 ppm). Common synonyms for benzene include benzol, cyclohexatriene, phenyl hydride, and coal tar naphtha.

Benzene is one of the world's major commodity chemicals. Its primary use (85% of production) is as an intermediate in the production of other chemicals, predominantly styrene (for styrofoam and other plastics), cumene (for various resins), and cyclohexane (for nylon and other synthetic fibers). Benzene is an important raw material for the manufacture of synthetic rubbers, gums, lubricants, dyes, pharmaceuticals, and agricultural chemicals.

Benzene is a natural component of crude and refined petroleum. The mandatory decrease of lead alkyls in gasoline has led to an increase in the aromatic hydrocarbon content of gasoline to maintain high octane levels and antiknock properties. In the United States, gasoline typically contains less than 2% benzene by volume, but in other countries the benzene concentration may be as high as 5%.

Because of its lipophilic nature, benzene is an excellent solvent. Its use in paints, thinners, inks, adhesives, and rubbers, however, is decreasing and now accounts for less than 2% of current benzene production. Benzene was also an important component of many industrial cleaning and degreasing formulations but now is replaced mostly by toluene, chlorinated solvents, or mineral spirits. Although benzene is no longer added in significant quantities to most commercial products, traces of it may still be present as a contaminant.

Because of its many uses, benzene is widespread in the environment. It is a component of both indoor and outdoor air pollution. Benzene levels measured in ambient air have ranged from less than 0.001 ppm in pristine rural areas to more than 0.1 ppm in urban areas. Sources of benzene in air are usually associated with chemical manufacturing or gasoline, including gasoline bulk-loading and discharging facilities and combustion engines (such as in automobiles, lawn mowers, and snow blowers). In almost all cases, benzene levels inside residences or offices are higher than levels outside. Benzene levels are also usually higher in homes with attached garages and those occupied by smokers. In the fall and winter when buildings are less-well ventilated, benzene levels are even higher. The Environmental Protection Agency (EPA) classifies benzene as a Group A* carcinogen and has estimated that a lifetime exposure to 0.004 ppm benzene in air will result in, at most, 1 additional case of leukemia in 10,000 people exposed. (EPA risk estimates assume there is no threshold for benzene's carcinogenic effects.)

Leakage from underground storage tanks and seepage from landfills or improper disposal of hazardous wastes has resulted in benzene contamination of groundwater used for drinking. Effluent from industries is also a source of ground-water contamination. EPA's Office of Drinking Water has estimated that lifetime exposure to a benzene concentration of 68 parts per billion (ppb) in drinking water would correspond to, at most, 1 additional cancer case in 10,000 people exposed. (The current EPA maximum contaminant level [MCL] for benzene in drinking water is 5 ppb.) In addition to being ingested, benzene in water can also be absorbed through wet skin and inhaled as it volatilizes during showering or laundering.

Persons who smoke one pack of cigarettes a day inhale a daily dose of approximately 1 milligram of benzene, which is about one-thirtieth of the daily amount inhaled by a worker exposed at the currently permissible workplace level.

* Group A consists of agents for which sufficient evidence supports a causal association between exposure and cancer in humans and in experimental animals.

Challenge

(1) Later, the patient in the case study tells you that his well water has always tasted "funny" and smells like "solvent." You learn that a chemical plant was adjacent to his property until 9 years ago when the company moved to another location. You are concerned about your patient's description of his drinking water, and you request that the state health department investigate the problem. The investigator contacts the chemical company that owns the abandoned site and learns that benzene is stored at the site in tanks that are above and below ground. Laboratory analyses of the patient's well water reveal an average concentration of 20 ppm benzene and traces of 1,1,1-trichloroethane and toluene.

What areas will you explore in your questioning to gauge the extent of the patient's exposure to benzene?

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Who's at Risk

- ☐ **Two to three million U.S. workers are at risk of benzene exposure.**
- ☐ **Alcohol and other drugs that induce the mixed function oxidase (MFO) enzymes may potentiate the effects of benzene.**

Workers employed in industries using or producing benzene have the greatest likelihood of exposure. The National Institute for Occupational Safety and Health (NIOSH) estimates that approximately two to three million workers in the United States may be exposed to benzene during refining operations; gasoline storage, shipment, and retail operations; chemical manufacturing; plastics and rubber manufacturing; shoe manufacturing; printing; and activities in chemical laboratories. A review of benzene exposure in the U.S. petroleum industry from 1978 to 1983 indicated that 87% of exposures were below an 8-hour time-weighted average (TWA) of 1 ppm and 98% were below 10 ppm.

In 1980, an estimated 37 million people in this country were exposed to benzene vapors at self-service gasoline stations. During gasoline pumping, atmospheric benzene levels up to 6.6 ppm have been measured, with a 6-hour TWA of 0.1 ppm. This risk has been lowered by installing vapor recapture devices on delivery hoses, which, if used properly, significantly reduce exposure. Catalytic converters have significantly reduced the benzene in automobile emissions.

Benzene is converted to toxic metabolites mostly by mixed-function oxidases (MFO) in the liver and bone marrow. MFO-inducing drugs (e.g., phenobarbital, alcohol) and certain chemicals (e.g., chlordane, parathion) may increase the rate at which toxic metabolites of benzene are formed. Theoretically, persons with rapidly synthesizing marrows—the fetus, infants and children, persons with hemolytic anemia or with agranulocytosis—are at increased risk.

Challenge

(2) Does the patient in the case study have any risk factors for the adverse effects of benzene? Is anyone else in the case at risk of benzene exposure or its adverse effects?

Biologic Fate

Benzene is absorbed rapidly by inhalation and ingestion, and slowly through intact skin. After a 4-hour exposure to approximately 50 ppm benzene in air, human volunteers absorbed about 50% of the amount inhaled.

Distribution of benzene to tissues is dependent on relative perfusion rates. In humans, approximately half of an inhaled dose is distributed to the liver and bone marrow. Benzene accumulation is slow in fat, but the total potential uptake is great because of benzene's high lipid solubility.

Absorbed benzene is metabolized primarily in the liver. Benzene metabolism initially involves oxidation, with phenol as the major metabolite. Further metabolic products formed by the introduction of hydroxyl groups on the aromatic ring include hydroquinone, catechol, and 1,2,4-trihydroxybenzene. These hydroxylated metabolites can be further oxidized to their corresponding quinones or semiquinones. Urinary excretion of small amounts of muconic acid, a straight-chain dicarboxylic acid, indicates that the benzene ring also is opened during metabolism.

Bone marrow is the main target organ of benzene toxicity. It contains the MFO enzymes necessary to metabolize benzene, and although benzene metabolism in bone marrow is not clearly understood, one or more benzene metabolites are suspected as responsible for the hematotoxicity. The metabolites may bind covalently to cellular macromolecules (e.g., proteins, DNA, and RNA), causing disruption of cell growth and replication. The rate of benzene metabolism in bone marrow is lower than that in the liver.

Approximately 50% of absorbed benzene is excreted unchanged via the lungs over a 36-hour period, depending on exercise level and amount of body fat. Respiratory elimination is triphasic, with approximate half-lives of 1 hour, 3 hours, and greater than 15 hours. Urinary excretion of metabolites, primarily phenol, is another important pathway for elimination. Most of the phenol is excreted in the form of sulfate esters and glucuronides. After a single exposure, urinary excretion of phenol and hydroquinone is highest within the first 24 hours and is essentially complete within 48 hours.

☐ **Benzene is absorbed well after inhalation or ingestion; in comparison, dermal absorption is slow.**

☐ **Benzene is metabolized in the liver and bone marrow.**

☐ **Benzene excretion occurs via the lungs and urine.**

Physiologic Effects

☐ **Benzene affects primarily the CNS and hematopoietic system.**

Benzene exposure affects the central nervous system (CNS) and hematopoietic system and may affect the immune system. Death due to acute benzene exposure has been attributed to asphyxiation, respiratory arrest, CNS depression, or cardiac dysrhythmia. Pathologic findings in fatal cases have included respiratory tract inflammation, lung hemorrhages, kidney congestion, and cerebral edema.

Central Nervous System Effects

☐ **At very high concentrations, benzene rapidly causes CNS depression, which can lead to death.**

Acute benzene exposure results in classic symptoms of CNS depression such as dizziness, ataxia, and confusion. General agreement that benzene itself is responsible for central nervous system effects, and benzene metabolite(s) are responsible for the observed blood dyscrasias, has evolved from temporal studies and the fact that agents known to alter benzene metabolism also alter benzene hematotoxicity.

Hematologic Effects

☐ **All three blood cell lines may be adversely affected by benzene.**

☐ **Pluripotential stem cells and lymphocytic cells are the probable targets of benzene toxicity.**

All three cell lines—erythrocytes, leukocytes, and platelets—may be affected by benzene to varying degrees. Benzene's most likely target is the DNA of the pluripotential stem and lymphocytic cells. Hematologic abnormalities such as anemia, leukopenia, thrombocytopenia, or pancytopenia may occur after chronic exposure. Potentially fatal infections can develop if granulocytopenia is present, and hemorrhage can occur as a result of thrombocytopenia. Paroxysmal nocturnal hemoglobinuria, a rare paraneoplastic disorder, has been associated with benzene exposure. Cytogenetic abnormalities of bone marrow cells and circulating lymphocytes have been observed in workers exposed to benzene, abnormalities not unlike those observed after exposure to ionizing radiation. Myelodysplastic effects also can be seen in the bone marrow of persons chronically exposed to benzene.

Anemia

☐ **Benzene-induced aplastic anemia is caused by chronic exposure at relatively high levels.**

Fatal aplastic anemia was first reported in benzene-exposed workers in the nineteenth century. Aplastic anemia is a condition caused by bone marrow failure, resulting in hypoplasia with an inadequate number of all cell lines. Generally, benzene-induced aplastic anemia is caused by chronic exposure at relatively high doses. No overt cytopenic effects have been observed in persons exposed at the previous workplace permissible exposure limit of

10 ppm. Severe aplastic anemia typically has a poor prognosis and can progress to leukemia, whereas pancytopenia may be reversible.

Leukemia

The causal relationship between benzene exposure and leukemia, which has been suspected for over 50 years, has only recently been accepted widely. Lack of adequate epidemiologic data and difficulty in producing hematologic carcinogenicity in animals impeded a consensus. Cohort studies of benzene-exposed workers in several industries (sheet rubber manufacturing, shoe manufacturing, rotogravure printing) have demonstrated significantly elevated risk of leukemia, predominantly acute myelogenous leukemia, but also erythroleukemia and acute myelomonocytic leukemia. For benzene-induced leukemia the latency period is typically 5 to 15 years after first exposure. Patients with benzene-induced aplastic anemia have been observed to progress to a preleukemic phase and develop acute myelogenous leukemia. However, a person exposed to benzene may develop leukemia without having aplastic anemia.

☐ **Benzene-induced leukemia has a usual latency period of 5 to 15 years and, in many cases, is preceded by aplastic anemia.**

Studies addressing the risk of leukemia associated with low-level benzene exposures have been inconclusive. Death certificates do not reveal increased leukemia mortality among workers potentially exposed to low levels of hydrocarbons and other petroleum products. However, in one recent case-control study, significantly more patients with acute nonlymphocytic leukemia were employed as truck drivers, filling station attendants, or in jobs involving exposure to low levels of petroleum products than among the controls.

Other Effects

Several reports relate benzene exposure to a variety of lymphatic tumors including non-Hodgkin's lymphoma and multiple myeloma. Although this is plausible, no scientific proof of a causal relationship exists. The association between exposure to benzene and development of nonhematologic tumors remains inconclusive.

☐ **The evidence is insufficient to indicate a causal relationship between benzene and nonhematologic tumors.**

Information on the reproductive toxicity of benzene in humans is meager. Benzene has not been proven teratogenic in humans or animals at doses that do not produce maternal toxicity.

☐ **Teratogenic effects due to benzene have been observed in animals only at high exposure levels.**

Clinical Evaluation

History and Physical Examination

In addition to a thorough medical history and physical examination, important factors in evaluating a patient potentially exposed to benzene include a detailed family history of blood dyscrasias including hematologic neoplasms, genetic hemoglobin abnormalities, bleeding abnormalities, and abnormal function of formed blood elements; an environmental history focusing on activities and possible sources of benzene exposure at home; and an occupational history, including past exposures to hematologic toxicants such as solvents, insecticides, and arsenic. A history of ionizing radiation exposure, medications, and smoking should also be explored.

Signs and Symptoms

Acute Exposure

☐ **Acute benzene exposure causes CNS depression.**

Acute benzene toxicity is characterized by central nervous system depression. Symptoms may progress from light-headedness, headache, and euphoria, to respiratory depression, apnea, coma, and death. Benzene concentrations of about 20,000 ppm are fatal to humans within 5 to 10 minutes.

"Benzol jag" is a term workers use to describe symptoms of confusion, euphoria, and unsteady gait associated with acute benzene exposure. Depending on the magnitude of the dose, persons who have ingested benzene may experience these effects 30 to 60 minutes after benzene ingestion. In one case report, an oral dose of 10 milliliters (mL) was reported to produce staggering gait, vomiting, tachycardia, pneumonitis, somnolence, delirium, seizures, coma, and death.

Chronic Exposure

☐ **Symptoms of chronic benzene exposure may be nonspecific, such as fatigue and anorexia.**

Early symptoms of chronic benzene exposure are often nonspecific but show marked individual variability. By the time a physician is consulted, the bone marrow may have been affected significantly. For example, conditions that first bring the patient to medical attention are typically fever due to infection or manifestations of thrombocytopenia, such as hemorrhagic diathesis with bleeding from the gums, nose, skin, gastrointestinal tract, or elsewhere.

The clinical picture of patients chronically exposed to benzene was described well in 1938 in a cohort study of about 300 workers in the rotogravure printing industry. At that time, ink solvents and thinners containing 75% to 80% benzene by volume were used in the pressroom. Initial physical examination of the workers was relatively unrevealing, but of those tested, 22 persons had severe hematologic abnormalities. Follow-up of the workers a year after exposure ceased suggested that the effects of benzene can persist or can evolve over time. Most patients recover after exposure ceases.

Laboratory Evaluation

Laboratory evaluation of benzene-exposed persons should include the following:

☐ **Hematologic abnormalities are the primary concern in benzene exposure.**

> CBC with differential, hematocrit, hemoglobin, erythrocyte count, erythrocyte indices (MCV, MCH, MCHC), and platelet count.

Plasma folate and vitamin B_{12} levels may be used to rule out megaloblastic anemia if the MCV is elevated.

The above laboratory tests will detect hematologic abnormalities that have been associated with relatively high levels of exposure to benzene. Persons with blood dyscrasias that persist after removal from exposure should be evaluated by a hematologist. Bone marrow aspiration and biopsy may be useful in narrowing the differential diagnosis in some cases.

Direct Biologic Indicators

Measurement of benzene in breath and blood can be useful in certain occupational settings. Because of benzene's relatively short biologic half-life, blood levels do not reflect cumulative body burden. A less invasive measurement of exposure in the workplace may be the benzene concentration in end-expired air. Studies show that 16 hours after an 8-hour exposure to benzene levels of 10 ppm and 1 ppm, steady-state exhaled benzene concentrations are 50 ppb and 10 ppb, respectively. However, these methods are not clinically useful for patients exposed to the low levels of benzene typically found in ambient air.

☐ **Measurement of benzene in blood and breath is generally not clinically useful in nonoccupational settings.**

☐ **Urinary phenol concentrations do not correlate with airborne benzene levels below 10 ppm.**

Urinary phenol concentrations generally correlate well with benzene exposure at concentrations above 10 ppm. Exposure to 10 ppm for 8 hours typically produces a postshift urinary phenol level of 45 to 50 milligrams per liter (mg/L). With exposure to air levels below 10 ppm, high background excretion of phenol from dietary and other sources can render urinary phenol levels unreliable. Unexposed persons rarely have urinary phenol levels greater than 20 mg/L.

Indirect Biologic Indicators

- ☐ **MCV and lymphocyte count may aid in the diagnosis of benzene toxicity.**
- ☐ **A bone marrow aspiration and biopsy will aid in identifying aplastic anemia.**

An increase in MCV and a decrease in total lymphocytes may be early signs of benzene toxicity. A finding of benzene-induced hematotoxicity in a patient should trigger consideration that this represents a sentinel event, indicating that other persons may have been similarly exposed.

If aplastic anemia is suspected, a bone marrow aspiration and biopsy should be performed. Aspiration of the marrow space often produces no sample (dry tap) in patients with aplastic anemia; however, a dry tap is not diagnostic of aplastic anemia; therefore, a biopsy specimen should be obtained as well and examined for architecture and cellularity. In aplastic anemia, only the empty reticular meshwork of the marrow is evident with fat cells replacing all or most of the hematopoietic tissues. Islands of residual hematopoiesis may be seen, but the overall cellularity typically is less than 25%. Chromosomal changes consistent with myelodysplasia are seen on cytogenetic analysis.

Challenge

(3) What should be included in the problem list of the patient described in the case study?

(4) Additional Information for the Case Study: A bone marrow aspiration reveals fibrous and fatty structures with very few spicules including mononuclear phagocytes, reticulum cells, and plasma cells. Rare promyelocytes and megaloblastic nucleated erythroid cells are present. No megakaryocytes are observed.

What differential diagnosis do the patient's hematologic results suggest?

(5) What additional laboratory testing would you recommend?

Treatment and Management

Acute Exposure

Treatment for persons acutely exposed to benzene is generally supportive and symptomatic. Immediate removal of the patient from exposure and administration of oxygen and cardiopulmonary resuscitation measures are the first consideration. In cases of ingestion, respiratory distress may indicate pulmonary aspiration of gastric contents.

Contaminated clothing and shoes should be removed from an exposed person as soon as possible. If the skin or eyes have contacted liquid benzene, immediately wash the exposed skin with soap and copious water, and irrigate the eyes with running water for 3 to 5 minutes or until irritation ceases.

In cases of ingestion, emesis is recommended in alert adult patients if less than 1 hour has passed since ingestion. However, if CNS or respiratory depression are present or likely, emesis is contraindicated. Care must be taken to avoid aspiration of stomach contents during vomiting because benzene can produce a severe chemical pneumonitis. Gastric lavage may be preferable to emesis if large amounts of benzene have been ingested or if the patient is seen more than 1 hour after ingestion. Activated charcoal decreases benzene absorption in experimental animals, and the benefits are likely to be similar in humans.

When medically indicated, epinephrine should be used cautiously with careful cardiac monitoring. Benzene is one of several solvents that may increase the susceptibility of the myocardium to the dysrhythmogenic effects of catecholamines.

☐ **There is no antidote for acute benzene poisoning.**

☐ **Treatment for benzene toxicity is supportive and symptomatic.**

Chronic Exposure

In treating persons chronically exposed to benzene, the most important actions are to remove the patient from the source of benzene exposure and to prevent further exposure. Benzene-induced depression of blood elements generally reverses after exposure is terminated. Chronically exposed patients whose hematologic results do not return to normal despite removal from exposure should be managed in consultation with a hematologist or oncologist. Chemotherapy and bone marrow transplants are therapeutic options for leukemia and aplastic anemia, respectively.

☐ **Once chronic exposure to benzene ceases, hematologic test results typically return to normal.**

Challenge

(6) What are some key considerations in the treatment for the patient in the case study?

(7) What is the prognosis for this patient? What follow-up care should he receive?

Standards and Regulations

Workplace

Air

☐ **The current permissible exposure limit for benzene is 1 ppm.**

In 1987, the Occupational Safety and Health Administration (OSHA) instituted a permissible exposure limit for benzene of 1 ppm, measured as an 8-hour time-weighted average (TWA), and a short-term exposure limit of 5 ppm (Table 1). These legal limits were based on studies demonstrating compelling evidence of health risk to workers exposed to benzene. The risk from exposure to 1 ppm for a working lifetime has been estimated to be 5 excess leukemia deaths per 1000 employees exposed. (This estimate assumes no threshold for benzene's carcinogenic effects.) OSHA has also established an action level of 0.5 ppm to encourage even lower exposures in the workplace.

The National Institute for Occupational Safety and Health (NIOSH) recommends an exposure limit of 0.1 ppm as a 10-hour TWA. NIOSH also recommends that benzene be handled in the workplace as a human carcinogen.

Table 1. Standards and regulations for benzene

Agency[*]	Focus	Level	Comments
ACGIH	Air-workplace	10 ppm	Advisory; 8-hour TWA[†]; suspected human carcinogen
NIOSH	Air-workplace	0.1 ppm	Advisory; 10-hour TWA
		1.0 ppm	15-min ceiling limit
OSHA	Air-workplace	1 ppm	Regulation; 8-hour TWA
		5 ppm	15-min STEL[§]
EPA	Drinking water	5 ppb	Regulation; maximum contaminant level
FDA	Food	N/A	Regulation; may be used only as a component of packaging adhesives

[*] ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration

[†] TWA (time-weighted average) = time-weighted average concentration for a normal workday and a 40-hour workweek to which nearly all workers may be repeatedly exposed.

[§] STEL (short-term exposure limit) = usually determined by a 15-minute sampling period.

Environment

Air

Benzene has been designated as a hazardous air pollutant under section 112 of the Clean Air Act. EPA has not promulgated a specific ambient air standard for benzene but has imposed restrictions designed to lower industrial emissions of benzene by 90% over the next 20 years. In addition, regulations have been proposed that would control benzene emissions from industrial solvent use, waste operations, transfer operations, and gasoline marketing. At gas stations, proposed rules would require new equipment restricting benzene emissions while dealers' storage tanks are being filled.

❑ **EPA restricts benzene emissions from specific point sources.**

Water

☐ **The maximum contaminant level of benzene in drinking water is 5 ppb.**

The National Primary Drinking Water Regulations promulgated by EPA in 1987 set a maximum contaminant level for benzene of 0.005 ppm (5 ppb). This regulation is based on preventing benzene leukemogenesis. The maximum contaminant level goal (MCLG), a nonenforceable health goal that would allow an adequate margin of safety for the prevention of adverse effects, is zero benzene concentration in drinking water.

Food

☐ **FDA prohibits the use of benzene in foods.**

Effective April 1988, the Food and Drug Administration has mandated that benzene can only be an indirect food additive in adhesives used for food packaging.

Challenge

(8) The lawyer for the family of the patient in the case study approaches you and asks you to establish causality between the patient's condition and the benzene in the drinking water. How would you do so?

Suggested Reading List

Reviews

Austin H, Delzell E, Cole P. Benzene and leukemia. A review of the literature and a risk assessment. Am J Epidemiol 1988;127(3):419-39.

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Marcus WL. Chemical of current interest–benzene. Toxicol Ind Health 1987;3(1):205-66.

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Runion HE, Scott LM. Benzene exposure in the United States, 1978-1983: an overview. Am J Ind Med 1985;7:385-93.

Risk Assessment

Rinsky RA, Smith AB, Hornung R, et al. Benzene and leukemia: an epidemiologic risk assessment. N Engl J Med 1987;316:1044-9.

Related Government Publications

Agency for Toxic Substances and Disease Registry. Toxicological profile for benzene. Atlanta: US Department of Health and Human Services, Public Health Service, 1989. NTIS report no. PB/89/209464/AS.

Environmental Protection Agency. Health effects assessment for benzene. Cincinnati, OH: US Environmental Protection Agency, Office of Health and Environmental Assessment, 1984. Report no. EPA/540/1-86/037.

Sources of Information

More information on the adverse effects of benzene and the treatment and management of benzene-exposed persons can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Benzene Toxicity* is one of a series. For other publications in this series, please use the order form on the back of page 21. For clinical inquiries, contact ATSDR, Division of Health Education, Office of the Director, at (404) 639-6204.

In addition to other resources, ATSDR has created a National Exposure Registry for benzene. This registry is one of a series mandated by the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA). ATSDR, in cooperation with the states, will establish and maintain national registries of (1) persons exposed to substances and (2) persons with serious illness or diseases possibly due to exposure. The registries will collect information on the effects of low-level exposures of long duration (i.e., the exposures typically found in populations surrounding hazardous waste sites) and the health outcomes for populations receiving a one-time, high-level environmental exposure (such as those experienced at chemical spill sites). The registries will facilitate the identification and subsequent tracking of persons exposed to a defined substance at selected sites and will coordinate the clinical and research activities involving the registrants. For further information on the benzene registry, please contact ATSDR Division of Health Studies, Office of the Director, at (404) 639-6200.

Answers to Pretest and Challenge Questions

Pretest questions are found on page 1; answers are in (3) through (7) below. Challenge questions begin on page 3.

(1) Some important areas to explore include amounts and duration of exposure from the following sources:

- water supply (ingestion)
- water supply (inhalation or dermal absorption during bathing and laundering)
- ambient air (fugitive emissions from the chemical plant during its operation and since it was abandoned 9 years ago)
- occupation (activities, conditions, and time spent as a diesel mechanic)
- workplace conditions (cleaning of machinery parts, solvents used, protective equipment worn, and the adequacy of ventilation)
- home environment (use of consumer products that might contain benzene, exposure to personal or passive cigarette smoke)

(For more information, see *Case Studies in Environmental Medicine: Taking an Exposure History,* ATSDR, October 1992.)

(2) Theoretically, a person could be at increased risk of benzene's adverse effects if he or she encountered agents or conditions that increased the rate of formation of toxic benzene metabolites through induction of the MFO system. Potential agents include MFO-inducing drugs (e.g., phenobarbital, alcohol); conditions include those causing rapid synthesis of bone marrow. The patient only occasionally drinks beer and did not take medications before his illness, and so he avoids the risk factors of alcohol and medications. However, if the patient is suffering from a hematologic abnormality, as his symptoms and laboratory evaluation suggest, he will have increased risk if benzene exposure continues.

Other persons in the case who may be at increased risk of benzene exposure are those who have had contact with the water supply for a prolonged period of time, although no data exist to quantitate the risk. Included are persons who have lived in the patient's household and members of the community who share the water supply. Community and household members who are at increased risk of benzene's adverse effects theoretically include those with rapidly synthesizing bone marrows and persons with increased MFO-mediated metabolism (e.g., heavy drinkers).

(3) The patient's problem list includes a clotting disorder, fatigue, ecchymoses and petechiae, and anorexia with concomitant weight loss.

(4) The hematology study reveals significant thrombocytopenia, leukopenia, and erythropenia. Pancytopenia is caused by the accelerated destruction or decreased production of all cell lines including red blood cells, white blood cells, and platelets. Bone marrow disorders are likely to be the cause, and could result from the following: drug and chemical toxicity (such as benzene toxicity), radiation, infection, nutrient deficiencies (e.g., vitamin B_{12} and folate), hypersplenism, and marrow replacement syndromes.

(5) Additional testing for the patient might include coagulation factors, evaluation for infectious agents, and assessment of nutrient status. Evaluation of the bone marrow should include a search for malignant cells. Cytogenetic abnormalities, if observed, may be helpful in the evaluation but are not definitive.

(6) The patient must be removed from exposure to benzene and other hematologic toxicants. His home water for drinking and personal purposes should be obtained from a source with no detectable level of

benzene. Work exposure to toxic chemicals must be carefully evaluated. Adequate nutrients (vitamins and protein source) in his diet should be assured. Care to prevent injury and bleeding must be exercised until proper blood coagulation (platelets and other factors) has returned, and the patient should be carefully monitored for infection in the event of severe granulocytopenia. Prophylactic antibiotics and blood transfusions should be avoided unless a significant deterioration of his condition becomes evident.

(7) The prognosis is generally good for the resolution of the macrocytosis. Although this patient has a significant aplastic anemia, it is possible for his bone marrow to recover slowly if the damage has not reached an irreversible stage. Supportive treatment will be needed for many months. Because of the continued risk of leukemia, the patient should receive medical surveillance consisting of regularly scheduled examinations and appropriate testing of hematologic function. The peripheral smear and blood count will permit monitoring of early changes of the patient's condition. Bone marrow biopsy should be repeated in a few weeks to confirm initial findings and observe an expected bone marrow recovery.

(8) One step in your quest to establish a causal relationship between benzene-contaminated home water and the patient's condition would be to further investigate competing causes of low blood counts for this patient (e.g., drugs, radiation exposure, family history), keeping in mind that most cases of aplastic anemia are idiopathic. You would also need to explore the patient's potential exposure to chemicals other than benzene that might cause hematologic disorders. Finally, assuming the patient's condition is due to benzene exposure, you would need to weigh the significance of benzene sources other than the drinking water. For example, the patient is a diesel mechanic and most likely has inhalation and dermal exposure to gasoline (which contains benzene) at work. You would need to determine the amounts of benzene each source might have contributed to the patient's exposure. (See answer number 1 above.)

For the patient in the case study, as for most exposure cases, it will not be an easy matter to establish causality, and there is no precedent for a person developing hematologic abnormalities from benzene in drinking water.

ATSDR July 1992
Case Studies in Environmental Medicine

19

Beryllium Toxicity

Environmental ALERT . . .

- ☑ ***Beryllium produces a range of health effects from sensitization without evidence of disease to clinically apparent pulmonary disease.***
- ☑ ***Chronic beryllium disease may be misdiagnosed as sarcoidosis.***
- ☑ ***New immunologic tests promise early detection of beryllium disease and differentiation from other interstitial lung diseases.***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. See page 17 for further information about continuing medical education credits and continuing education units.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

A 14-year-old child, daughter of a dental technician, with cough, wheezing, and low-grade fever

A mother brings her 14-year-old daughter to you for consultation. The patient has developed a troublesome cough and sometimes at night cannot catch her breath. The child's cough has worsened with increase in sputum production and chest discomfort. Last night she had a particularly rough time, but she had no wheezing or fever. Chart review reveals no history of asthma or allergies. The patient's height and weight are appropriate for her age; her two siblings, aged 12 and 6 years, are in good health. History of previous illness reveals three episodes of otitis media but no other significant illness. There is no history of eczema or food intolerance.

In response to your questions, the mother tells you that her husband, a dental technician, has been diagnosed with sarcoidosis. He recently had flu-like symptoms similar to those of his daughter including fatigue, nasal congestion, sneezing, and cough. Although her husband, who smokes cigarettes, has had a cough for several years, the mother states that her daughter developed symptoms a few days after her husband's latest bout. She wonders if her husband's sarcoidosis could have been transmitted to their daughter.

Examination shows a cheerful girl in no acute distress. Her temperature today is 100°F, respiratory rate is 24 without retractions or audible wheezing, and her pulse is 90 and regular. Significant findings include a mildly inflamed pharynx and anterior cervical lymph nodes that are slightly enlarged and mildly tender. Tympanic membranes are clear. Auscultation of the lungs reveals mild and diffuse expiratory wheezing with occasional rhonchi. Results of cardiac and abdominal examinations are normal. Chest X ray shows minimal peribronchial thickening and is otherwise normal.

Pretest

(a) Construct a problem list and a differential diagnosis for the daughter.

(b) What further questions might you ask about the father?

(c) What is the most likely diagnosis for the daughter?

Answers can be found on page 14 and 15.

Exposure Pathways

☐ **Because of its unique properties, beryllium is used in many high-technology consumer and commercial products.**

☐ **Burning of coal is probably the greatest source of environmental beryllium contamination.**

Pure beryllium, one of the lightest metals known, is a hard, grayish material obtained from the mineral rocks bertrandite and beryl. Gem quality beryl is known as either aquamarine or emerald. Although production of beryllium has increased only modestly in the United States in the past 2 decades, the uses of beryllium have expanded. Beryllium has important uses in the defense and electronics industry, especially applications in which fatigue and corrosion resistance, insulation, and nonmagnetic and lightweight qualities are desired.

Occupational exposure to beryllium (as a dust or fume) can occur where it is mined, processed, or converted into metal, alloys, and chemicals. The United States is the leading producer and consumer of beryllium and its alloys. Pure beryllium metal is used in aircraft disc brakes, X-ray components, space-vehicle optics and instruments, aircraft/satellite structures, missile parts, nuclear-reactor neutron reflectors, nuclear weapons, fuel containers, precision instruments, rocket propellants, navigational systems, heat shields, and mirrors. Beryllium alloys also have many uses, including electrical connectors and relays, springs, precision instruments, aircraft engine parts, nonsparking and nonmagnetic tools, computers, ceramics, submarine cable housings and pivots, wheels and pinions, and dental castings. Dental prostheses are shaped by grinding the structural elements, which are often made of beryllium alloy.

Beryllium oxide is the material of choice for many high-technology applications in which heat resistance is imperative. Applications include ceramics, electronic heat sinks, electrical insulators, microwave oven components, gyroscopes, military vehicle armor, rocket nozzles, crucibles, thermocouple tubing, and laser structural components.

Although beryllium is a naturally occurring substance, the major source of its emission into the environment is the combustion of fossil fuels (primarily coal), which releases beryllium-containing particulates and fly ash into the atmosphere. The open pits in Utah, where bertrandite is mined, also cause high airborne levels locally. Mantles of some camping lanterns emit small amounts of beryllium during initial use. Tobacco smoke also is a minor source of beryllium exposure. Beryllium is relatively water insoluble and adsorbs tightly to soils. It has been found in various foodstuffs, but bioaccumulation in the food chain is not significant.

Who's at Risk

There are no accurate estimates of the number of workers exposed to beryllium; however, we know that workers potentially exposed are those engaged in smelting, metal machining, and reclaiming scrap alloys, as well as those in high-technology industries such as aerospace, nuclear, telecommunications, and computer industries. The mining of beryllium ore has not been associated with beryllium disease (acute or chronic); however, the relationship has not been studied systematically. Inhaling metallic beryllium, beryllium oxide, beryllium-copper alloys, or beryllium salts can cause beryllium disease.

Beryllium disease was first noted in the 1930s in workers exposed to beryllium-containing phosphors in the fluorescent lamp industry. Industry standards and environmental controls for beryllium were established in the 1950s. Although acute beryllium disease occurs rarely today, chronic beryllium disease (berylliosis) continues to occur in industries where beryllium and its alloys are smelted, fabricated, and machined. The terms *acute* and *chronic*, used to describe beryllium disease, refer to disease processes, rather than types of exposure. Acute beryllium disease manifests as pulmonary inflammation, whereas chronic beryllium disease is typically a progressive pulmonary granulomatosis.

Low, seemingly trivial exposures to beryllium may be important in causing beryllium disease. Chronic beryllium disease has been found in persons living near a plant using beryllium, although neighborhood cases have decreased considerably since industry control measures were instituted. As recently as 1991, a case of chronic beryllium disease due to secondary contamination was reportedly caused by a family member's exposure to beryllium from a worker's clothing.

A small percentage of exposed persons (1% to 3%) develop beryllium hypersensitivity and chronic disease. (Hypersensitivity to beryllium can be demonstrated by in vitro proliferative responses of lymphocytes obtained through blood or bronchoalveolar lavage.) Some workers manifest this cellular immune response even if they work in areas where beryllium air concentrations are found to be below the recommended workplace exposure limits. Sensitization has been reported in security guards, secretaries, and custodial staff who work at facilities using beryllium.

No correlation has been found between smoking and increased incidence of beryllium disease. However, inhalation of beryllium does appear to alter the ability of the lungs to clear other inhaled agents.

☐ **Most significant exposures to beryllium occur in the occupational setting.**

☐ **A small percentage of the population is hypersensitive to beryllium.**

☐ **Chronic beryllium disease has been reported recently in a household contact of a beryllium worker.**

Challenge

Additional information for the case study: Because he is concerned about the care he is receiving from another doctor, the father of the patient in the case study asks you to render a second opinion on his condition. During examination, you perform a local excision to biopsy an ulcer on his hand. The biopsy reveals noncaseating granulomas. The biopsy result and a review of the chest radiograph and patient history lead you to include chronic beryllium disease in the differential diagnosis.

(1) How might the father have come in contact with beryllium?

(2) Could the father pass beryllium to other family members by contact or by coughing and sneezing?

Biologic Fate

- ☐ **Inhaled beryllium is solubilized in the lungs and distributed primarily to bone, liver, and kidneys.**
- ☐ **Contact of beryllium with broken skin can lead to systemic absorption.**
- ☐ **Most beryllium is excreted in the urine.**

Beryllium exposure occurs primarily by inhalation and contact through broken skin. After inhalation, particles containing beryllium are deposited in the respiratory tract, solubilized upon contact with respiratory epithelium, and absorbed into the bloodstream. Solubilized beryllium may bind to the phosphate in plasma proteins, forming a complex that is engulfed by macrophages. The pulmonary half-life of beryllium ranges from several weeks to 6 months, although beryllium has been detected in the lungs of persons with chronic beryllium disease decades after the exposure has ceased.

Ingested beryllium is presumed to be solubilized in the acidic milieu of the stomach and absorbed predominantly from the stomach. Beryllium absorption rates vary widely and correspond to gastric emptying time. In the intestinal fluid, a beryllium-protein complex forms and is eliminated. Ingested beryllium is not thought to be associated with disease.

Beryllium is not absorbed through intact and uninjured skin. However, significant amounts can be absorbed dermally through burns, abrasions, and open wounds. Local deposition and systemic absorption can result from accidental inoculation by beryllium splinters.

Beryllium and its compounds are not biotransformed but remain as Be^{+2} in the body. The highest levels of beryllium are found in bone; lesser amounts are distributed to the liver and kidneys. Placental crossing occurs only to a small extent.

Inhaled or ingested beryllium is excreted slowly. The renal system removes more than 90% of absorbed beryllium, but less than 1% is excreted within the first day. Plasma beryllium does not cross the glomerular membrane and is eliminated through the renal tubules. Levels in the urine are highly variable due to differing compartmental clearance rates; beryllium can take months to years to be removed from pulmonary lymph nodes and bone. The metal has been found in the urine as long as 10 years after cessation of exposure.

Physiologic Effects

Respiratory Effects

Two distinct mechanisms of lung injury can result from beryllium exposure. In acute disease, beryllium acts as a direct chemical irritant, causing a nonspecific inflammatory reaction. In chronic disease, which occurs in susceptible persons, a cell-mediated, delayed hypersensitivity reaction is involved. Inflammatory acute disease can progress to granulomatous chronic beryllium disease.

Acute beryllium lung disease has been almost completely eliminated in the United States. The U.S. Beryllium Case Registry (maintained by the National Institute for Occupational Safety and Health [NIOSH]) admitted only one case of acute disease from 1975 to 1980. Acute disease manifests as inflammation of the upper or lower respiratory tract or both. Acute and subacute bronchitis may occur, but the most serious complication is chemical pneumonitis. Acute disease can appear suddenly after short exposure to high concentrations or progress slowly after longer exposure to lower concentrations. Pneumonitis or bronchitis induced by inhaling beryllium is histologically identical to these diseases when caused by other pulmonary irritants. A dose-response relationship is suspected in the case of beryllium, but the data are not adequate to allow clarification.

Chronic beryllium disease is a granulomatous, interstitial inflammation affecting primarily the lungs, although granulomas also have been found in the liver, spleen, heart, and lymph nodes. The most common manifestation is chronic interstitial pneumonitis with infiltration of lymphocytes, histiocytes, and plasma cells. This interstitial pneumonitis is usually, but not invariably, associated with noncaseating granulomas ranging from indistinct collections of epithelioid cells to well-formed granulomas. Less often, one finds a predominance of well-formed granulomas with only focal, mild interstitial changes. Emphysema is common in chronic disease.

☐ **In acute disease, beryllium acts as a chemical irritant.**

☐ **In chronic disease, beryllium initiates a delayed-type hypersensitivity reaction in the lungs.**

☐ **The most common histology in chronic beryllium disease is granulomatous interstitial pneumonitis.**

Recent immunologic evidence suggests that the key pathogenic event in chronic disease is a beryllium-specific cellular immune response in the lungs. Investigators have found elevated helper:suppressor T-cell ratios in the pulmonary lymphocyte population. These helper T cells demonstrate an antigen-like response to beryllium, which is likely to be in the form of a beryllium-protein conjugate. The in vivo sensitization can be detected by the in vitro lymphocyte transformation test in bronchoalveolar lavage and in peripheral blood.

Dermal Effects

☐ **Skin contact with beryllium can cause ulceration and subcutaneous granulomas.**

Skin contact with soluble beryllium compounds can induce beryllium sensitization and cause contact dermatitis. Beryllium-containing particles that lodge in a worker's skin can cause skin ulceration; biopsy reveals noncaseating granulomas at the site of injury. There is no evidence that pulmonary disease can result from isolated dermal contact with beryllium.

Carcinogenic Effects

☐ **On the basis of animal studies, airborne beryllium is considered a potential human carcinogen.**

The potential for carcinogenicity due to beryllium depends on the exposure route. Inhalation of beryllium compounds currently is considered by the Environmental Protection Agency (EPA) to be potentially carcinogenic in humans because lung tumors have been induced in experimental animals by this route. Several epidemiologic studies have attempted to clarify the cancer-causing effects in humans, but the published studies have drawn conflicting conclusions. Most recent data suggest that beryllium workers are at increased risk of lung cancer.

Challenge

(3) What organ systems should be evaluated if beryllium exposure is suspected?

Clinical Evaluation

History and Physical Examination

Initial evaluation of a patient with a history of beryllium exposure includes a thorough occupational and environmental history, medical history, physical examination, chest X ray, pulmonary function tests, blood chemistries, and complete blood count. The beryllium-stimulated lymphocyte transformation test (described on page 9) can be used to detect early stages of beryllium disease and to lend specificity to the clinical diagnosis. During the medical history and physical examination, particular attention should be focused on the skin and respiratory tract.

- ☐ **If beryllium exposure is suspected, the skin and respiratory tract should be examined carefully.**
- ☐ **In chronic beryllium disease, the time between initial exposure and clinical disease can range from months to 30 years.**

The latency between exposure and detectable disease averages 10 to 15 years, with a range of several months to 30 years. Evidence suggests that at least some beryllium disease cases are triggered or exacerbated by physiologic stress such as surgery, pregnancy and lactation, and intercurrent illness.

Signs and Symptoms

Acute

The onset of pneumonitis due to beryllium exposure can be abrupt or insidious and the progression, rapid or slow. Symptoms include progressive dyspnea, cough, substernal chest pain, anorexia, and fatigue. Common signs are tachycardia, rales, and sometimes cyanosis. Conjunctivitis, periorbital edema, nasopharyngitis, and tracheobronchitis also have been reported. Acute beryllium disease is rarely encountered today.

- ☐ **Acute beryllium toxicity causes a nonspecific inflammatory reaction in the respiratory tract.**

Chronic

There is a wide spectrum of physical findings in patients chronically exposed to beryllium. Some patients are asymptomatic but have an abnormal chest radiograph or positive beryllium-stimulated lymphocyte transformation test. The most common symptom is exertional dyspnea, which is usually progressive. Other complaints may include cough, fatigue, weight loss, chest pain, and arthralgias. Bibasilar rales are detected frequently. Other findings may include lymphadenopathy, skin lesions, hepatosplenomegaly, and clubbing. Signs of pulmonary hypertension, cor pulmonale, and right ventricular failure may be present in end-stage disease.

- ☐ **Exertional dyspnea is the most common symptom of chronic beryllium disease.**

Beryllium can cause contact dermatitis. A single dermal exposure can also sensitize the skin to future exposures. If beryllium becomes embedded in the skin, it can cause delayed healing, ulcers, and granuloma formation. Although rare, cutaneous granulomas can be a manifestation of the systemic process of chronic beryllium disease. They are not necessarily related to direct dermal contamination.

Differential Diagnosis

☐ **Chronic beryllium disease continues to be misdiagnosed as sarcoidosis.**

The differential diagnosis for interstitial and granulomatous lung disease is long. Conditions that may resemble chronic beryllium disease include tuberculosis, fungal disease, asbestosis, silicosis, hypersensitivity pneumonitis, pulmonary hemosiderosis, lymphangitic spread of carcinoma, and sarcoidosis. Of these, the clinical features of sarcoidosis are most similar to the characteristics of chronic beryllium disease (Table 1). Although each disease possesses characteristic clinical features, no feature has proved adequately sensitive and specific to be pathognomonic. Chronic beryllium disease tends to have less prominent extrapulmonary manifestations. For example, to date, no patient with chronic beryllium disease has developed uveitis, uveoparotid fever, cranial or peripheral nerve involvement, or cystic bone lesions—conditions that have affected patients with sarcoidosis. Furthermore, chronic beryllium disease is progressive and often requires lifelong corticosteroid therapy to slow its course. Spontaneous remission of chronic beryllium disease has been reported to occur after cessation of exposure, but this is rare.

Table 1. Comparison of clinical features—sarcoidosis and chronic beryllium disease

Feature	Sarcoidosis	Chronic beryllium disease
Hilar adenopathy	Common	Less common*
Erythema nodosum	Common in acute stage	Absent
Parotid involvement	May be present	Absent
Bone changes	Present in chronic stage	Absent
Response to therapy	Good	Variable†

* About 30% to 40% of patients with chronic beryllium disease exhibit hilar adenopathy.

† Chronic beryllium disease is often managed well with corticosteroids, but some patients do not respond to this treatment and experience progressive fibrosis.

Laboratory Evaluation

☐ **Immunologic tests may assist the clinician in early diagnosis of chronic beryllium disease.**

Until recently, there was no diagnostic test for beryllium disease. Both atomic absorption spectrophotometry and mass spectrometry, which historically were used to detect and measure beryllium in biopsy specimens, are unsatisfactory. Spectrometric results correlate poorly with severity of pathology and can be within normal limits in some patients with disease. Likewise, elevated blood and urine beryllium levels signify only exposure to beryllium at an indeterminable time; absence of detectable urinary beryllium does not exclude significant exposure. Diagnosis, therefore, has been based traditionally on compatible clinical findings and laboratory results, pulmonary function defect, typical biopsy, and exposure potential.

A recently available in vitro assay, the beryllium-stimulated lymphocyte transformation test, may aid in confirming diagnosis and permit screening of patients for subclinical disease. The lymphocyte transformation test, used with beryllium, appears to be both specific and sensitive for beryllium disease. In affected patients, the helper T cells retrieved from bronchoscopic lavage or peripheral blood, when cultured in a bath of beryllium sulfate, yield a growth response that is typical of antigen-stimulated hypersensitivity reactions. Similar cells from patients with sarcoidosis or other pulmonary diseases do not demonstrate a proliferative response.

In some patients with chronic beryllium disease, serum chemistry studies show increased total protein due to elevated globulins, hyperuricemia, elevated erythrocyte sedimentation rate, elevated liver enzymes, hypercalcemia, and occasionally, elevated hematocrit. Only a small percentage of patients with beryllium toxicity have elevated serum angiotensin-1-converting enzyme activity.

Pulmonary evaluation for chronic beryllium disease, as for all interstitial lung diseases, includes chest X ray, pulmonary function tests, arterial blood gas measurements, and possibly bronchoscopy with tissue biopsy and lavage analysis for cell count, differential, and lymphocyte count. Chest radiograph findings may include diffuse infiltrates and hilar adenopathy, but can be negative. Infiltrates may be granular, diffuse linear, or small nodules. Hilar adenopathy, noted in 30% to 40% of patients, is usually mild, bilateral, and associated with parenchymal infiltrates. Severe disease may show interstitial fibrosis, honeycombing, and formation of conglomerate masses. Pleural thickening and pneumothorax can occur but are unusual.

Challenge

(4) What steps would you take to evaluate the condition of the daughter in the case study?

(5) What steps will be necessary to evaluate her father's condition?

Treatment and Management

- ☐ **Corticosteroid therapy is the primary treatment modality for chronic beryllium disease.**
- ☐ **An estimated 30% of patients with chronic beryllium disease die from complications directly attributable to their disease.**

Although there is little scientific evidence that cessation of exposure alters the course of beryllium disease once it is manifest, exposure cessation should be the first goal of management. For patients with chronic beryllium disease, corticosteroid therapy is the primary treatment modality. Corticosteroids provide symptomatic relief and improve lung function; they are required lifelong for most patients. When symptoms are controlled, an alternate day, single-dose regimen can be tried. Alternate-day doses usually range from 20 mg to 40 mg prednisone; occasionally up to 80 mg is required for short periods. More aggressive disease may require even higher daily doses of corticosteroids. There is no cure, and spontaneous remissions occur rarely.

Supplemental oxygen may be necessary to correct hypoxemia associated with chronic beryllium disease. Right ventricular failure and its complications are late-stage sequelae. Severe cough may require restricting physical activity. Pneumothorax can occur. Emphysema and pulmonary fibrosis, which are common in long-term disease, can prove poorly responsive to corticosteroids. As with chronic lung disease of other etiologies, one should be vigilant for bacterial respiratory infections and should treat infections promptly with antibiotics when indicated. Patients should be immunized against pneumococcus and influenza and counseled to avoid exposures to other substances that cause lung injury, including cigarette smoke.

Responses to therapy vary. In some cases, the disease symptoms appear mild at diagnosis, progress minimally, and are controlled well with corticosteroids. In others, the course is increasingly severe and controlled poorly by corticosteroids. Reviewers of 130 pathologic specimens obtained from patients in the U.S. Beryllium Case Registry concluded that the greater the degree of interstitial infiltration present, the worse the clinical course and prognosis. Persons demonstrating a predominance of well-formed granulomas and minimal interstitial fibrotic changes had a more benign course and better prognosis. Investigators found no correlation between histology and responsiveness to steroids, nor between length of the latency period and type of histology manifested. It is estimated that 30% of patients with chronic beryllium disease die from complications directly attributable to their disease.

Careful irrigation and débridement are recommended for wounds potentially contaminated with beryllium. Complete excision is curative for beryllium-contaminated injury sites that demonstrate delayed healing, ulceration, and granuloma formation. The main treatment for contact dermatitis associated with beryllium salt exposure is cessation of exposure.

Challenge

(6) What treatment will you recommend for the daughter in the case study?

(7) The father's beryllium-stimulated lymphocyte transformation test was abnormal and consistent with chronic beryllium disease. How will you treat and manage the father's condition?

Standards and Regulations

The standards and regulations for beryllium are summarized in Table 2. EPA considers beryllium a probable human carcinogen.

Workplace

Air

The Occupational Safety and Health Administration (OSHA) regulation for beryllium and its compounds is an 8-hour time-weighted average (TWA) of 2 micrograms (as beryllium) per cubic meter of air (2 $\mu g/m^3$). An employee should not be exposed to a concentration of beryllium and beryllium compounds above 5 $\mu g/m^3$. The 30-minute maximum peak level is 25 $\mu g/m^3$. NIOSH recommends that beryllium be treated as a potential human carcinogen and advises a 10-hour TWA not to exceed 0.5 $\mu g/m^3$.

Environment

Air

Beryllium has been designated a hazardous air pollutant under the Clean Air Act. According to EPA regulation, beryllium emissions cannot exceed 10 grams in a 24-hour period. Ambient air concentrations averaged over a 30-day period in the vicinity of stationary sources must not exceed 0.01 μg/m^3.

Water

The EPA advisory for beryllium in water is less than 68 nanograms per liter (ng/L) for consumption of 2 liters (L) of ambient water.

Table 2. Standards and regulations for beryllium

Agency[*]	Focus	Level	Comments
ACGIH	Air-workplace	2 μg/m^3	Advisory; TLV-TWA[†]
NIOSH	Air-workplace	0.5 μg/m^3	Advisory; 10-hr TWA
OSHA	Air-workplace	2 μg/m^3 5 μg/m^3 25 μg/m^3	Regulation; PEL[§] as TWA Regulation; Ceiling Regulation; STEL[¶] 30-min. maximum peak
EPA	Drinking water	68 ng/L for consumption of 2L	Advisory
	Air	10 g 24-hr period	Regulation

[*] ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration

[†] TLV-TWA (Threshold Limit Value-Time-Weighted Average) = Time-weighted average concentration for a normal workday and a 40-hour workweek to which nearly all workers may be repeatedly exposed.

[§] PEL (Permissible Exposure Limit) = Highest level of beryllium in air to which a worker may be exposed, averaged over an 8-hour workday.

[¶] STEL (Short-Term Exposure Limit) = usually determined by a 15-minute sampling period.

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Answers to Pretest and Challenge Questions

Pretest

Pretest questions are found on page 1. Challenge questions begin on page 4.

(a) The patient's problem list includes productive cough, wheeze, and low-grade fever. The most likely causes to consider for this patient's condition are reactive airway disease (asthma, rhinitis, or postnasal drip), an infectious process (viral or bacterial bronchitis or pneumonia), and chemical irritation (cigarette smoke or air pollution). Psychogenic etiology should also be considered. Less likely considerations include bronchiectasis, congenital abnormalities, foreign-body aspiration or other aspiration syndromes, cystic fibrosis, or tracheomalacia- bronchomalacia.

(b) Initially, you would want to know the father's general state of health, his full work history, habits of cigarette smoking, and history of respiratory problems. You may also wish to explore his hobbies and home environment. As a dental laboratory technician, the father may be at risk of exposure to beryllium (casting and grinding alloys used in dental prostheses), as well as to mercury (mixing dental amalgams). Chronic cough is a common symptom of chronic beryllium disease, which can be misdiagnosed as sarcoidosis unless specifically tested for.

(c) The most likely diagnosis for the patient is bronchitis. Wheezing, if present, could be a complication of bronchitis, or it could be a new onset of asthma triggered by infection or exacerbated by cigarette smoke from her father's cigarettes.

Workers casting or grinding beryllium can expose members of their households to beryllium dust brought home on workers' hair, skin, and clothes. These household members have developed chronic beryllium disease. On the basis of her signs and symptoms, it is unlikely that the patient has a beryllium-related disease. However, if she visits her father's workplace or if he does not change workclothes before leaving the workplace, she should be considered at risk.

Challenge Answers

(1) Beryllium alloy is used in some dental prostheses. If the father or his laboratory coworkers cast or machine-grind these prostheses, it is possible that beryllium from the workplace contaminated his hand wound. He should be carefully questioned about possible sources of beryllium exposure.

(2) There is no evidence to suggest that beryllium toxicity or disease can be passed by body fluids, coughing, or sneezing. To ensure that beryllium is not brought home from the workplace through beryllium-contaminated clothes and skin, you should discuss with the father proper workplace hygiene including changing clothes and showering before leaving the workplace. You should also take steps to determine if others in the workplace are exposed to beryllium.

(3) Chronic beryllium disease manifests almost solely in the lungs. If beryllium becomes embedded in skin, ulceration and poor wound healing can ensue.

(4) For the daughter, initial evaluation includes a careful history, thorough physical examination, and a chest X-ray. The history suggests an infectious process and, given the clinical picture, no other laboratory tests are recommended at this time. If her respiratory symptoms become chronic, she should be reevaluated. Asthma should be considered and, if her reevaluation suggests an interstitial lung disease, the blood beryllium-stimulated lymphocyte transformation test may be used for screening.

(5) Due to proven beryllium exposure, the father is a candidate for a more complete evaluation for beryllium toxicity. An abnormal blood beryllium-stimulated lymphocyte transformation test would indicate an increased probability that both the cutaneous and pulmonary abnormalities are due to beryllium exposure. A negative blood test, however, would not exclude the diagnosis of chronic beryllium disease. If the blood test is negative, consideration should be given to a bronchoscopy for lung tissue biopsy and bronchoalveolar lavage lymphocyte transformation test. (Note: The presence of macrophages in the lavage specimen of smokers can render the lavage test inconclusive.)

(6) The treatment for bronchitis is supportive care and should include rest, air humidification, and avoidance of noxious stimuli such as cigarette smoke. Antibiotics should be used if bacterial bronchitis is strongly suggested by the clinical course or is proven by reliable laboratory techniques. Given the sleep disturbance experienced by this patient, consideration may be given to bronchodilator therapy such as an inhaled β_2 agonist. If the patient's clinical course suggests asthma, treatment should be tailored to her needs.

(7) The father has chronic beryllium disease and a beryllium-induced skin ulceration. The first therapeutic effort should be to remove him from further exposure to beryllium. Values should be obtained for the following baseline tests: pulmonary function tests, carbon monoxide diffusion, and arterial blood gases. Corticosteroid therapy should be instituted.

The father should be reevaluated periodically to assess whether he has responded to corticosteroids, and to taper the dose to the minimum needed to control symptoms and maintain physiologic improvement. He should also be monitored for potential long-term steroid side effects. Excision of the cutaneous lesion should prove curative for the skin condition, but lifelong corticosteroid therapy will most likely be required for the lung condition.

Because the father may represent a sentinel case, the local health department should be notified. To prevent further exposures, the patient's workplace should be evaluated. Notification of OSHA or a request for a NIOSH health hazard survey may be warranted.

Sources of Information

More information on the adverse effects of beryllium and treating and managing cases of exposure to beryllium can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Beryllium Toxicity* is one of a series. For other publications in this series, please use the order form on the back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of the Director, at (404) 639-6204.

ATSDR June 1990

Case Studies in Environmental Medicine

10

Cadmium Toxicity

Environmental ALERT . . .

☑ ***Prevention is the key to managing cadmium exposure; no effective treatment for cadmium toxicity exists.***

☑ ***Nutritional deficiencies can increase the risk of cadmium toxicity.***

☑ ***Cadmium affects primarily the renal and skeletal systems.***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. The Agency for Toxic Substances and Disease Registry (ATSDR) and the Centers for Disease Control (CDC) designate this continuing medical education activity for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association and 0.1 continuing education units for other health professionals. See pages 21 to 23 for further information.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

Low back pain and waddling gait in a 60-year-old woman

A 60-year-old woman comes to your office with complaints of low back pain, which is causing progressive difficulty in walking. The pain has gradually increased since the onset of menopause 5 years ago. This discomfort is especially noticeable after prolonged sitting.

Social history reveals that the patient has been a housewife since her marriage 38 years ago. Her husband, who is in good health, owns and operates a small retail shop in their home. The patient has been making jewelry for sale in her husband's shop and as a hobby for about 35 years. They have two adult sons who are in good health.

The patient denies a personal or family history of kidney disease, hypertension, diabetes mellitus, or cardiovascular disease; she also denies history of back trauma or weight loss. She has smoked one to two packs of cigarettes a day for the past 40 years. She does not take estrogens, calcium supplements, vitamins, or other medications.

On examination you find a thin female with a slightly stooped posture and a waddling gait. Blood pressure is 120/70. Her teeth have a yellow discoloration above the crown, and her fingernails are stained with nicotine. She is anosmic on cranial nerve examination. Results of cardiovascular and abdominal examination are normal. The lower lumbar spine is tender to percussion, but the patient does not complain of pain on straight leg raising. Her deep tendon reflexes are intact, and the remainder of the physical examination, including neurologic testing, is normal. Sensation and strength are normal in legs and feet. Range of motion is normal in hips and knees.

Initial laboratory data include a urinalysis showing 3^{+} proteinuria and glycosuria. BUN, creatinine, and albumin levels are normal. Roentgenograms of the pelvis and lumbosacral spine reveal pseudofractures and other evidence of severe osteomalacia and mild osteoporosis. There are no osteolytic or osteoblastic lesions.

Pretest

(a) What should be included on the patient's problem list?

(b) What additional information would be helpful in diagnosing this woman's condition?

(c) What further tests, if any, would you recommend?

(d) What treatment would be appropriate for this patient?

Answers to the Pretest are included in Challenge answers (6) through (9) on page 19.

Exposure Pathways

- **In the general population, exposure to cadmium occurs primarily by eating crops grown in contaminated soil and seafood.**
- **Airborne cadmium sources include combustion of fossil fuels, incineration of municipal waste, and smelter emissions.**

Pure cadmium is a silver-white, lustrous metal, but cadmium in this form is not common in the environment. It is most often encountered in the earth's crust combined with chlorine (cadmium chloride), oxygen (cadmium oxide), and sulfur (cadmium sulfide). Cadmium oxide also exists as small particles in air (fume), the result of smelting, soldering, or other high-temperature industrial processes. Most cadmium used in the United States is obtained as a byproduct of the smelting of zinc, lead, or copper ores. Cadmium is used mainly in metal plating; in producing pigments, batteries, and plastics; and as a neutron absorbant in nuclear reactors.

Foods are the most important source of cadmium exposure for the general population. Low levels of cadmium are found in basic foodstuffs, especially grains, cereals, and leafy vegetables, which readily absorb naturally occurring cadmium or cadmium in soil contaminated by sewage sludge, fertilizers, and polluted groundwater. In 1946, the inhabitants of the Jintzu River basin in Japan were afflicted with a disease characterized by pain and bone fractures (called itai-itai or ouch-ouch disease), which was caused by high levels of cadmium in water and rice, the result of using water contaminated by discharges from a local zinc-mining operation. Cadmium bioaccumulates in the food chain; consequently, ingestion of animal internal organs, such as liver and kidneys, and some types of fish and shellfish may result in increased exposure.

The greatest sources of airborne cadmium are burning fossil fuels such as coal or oil, and incineration of municipal waste such as plastics and nickel-cadmium batteries. Cadmium may also escape into the air from zinc, lead, or copper smelters, and from iron and steel production facilities. Like most plants, tobacco contains cadmium, which is inhaled in cigarette smoke.

Cadmium concentrations in drinking water supplies are typically less than 1 microgram per liter (µg/L) or 1 part per billion (ppb). Groundwater seldom contains high levels of cadmium unless it is contaminated by mining or industrial wastewater, or seepage from hazardous waste sites. Soft or acidic water tends to dissolve cadmium and lead from water lines; cadmium levels are increased in water stagnating in household pipes. These sources have not caused clinical cadmium poisoning, but even low levels of contamination presumably contribute to the body's accumulation of cadmium.

Cadmium is a component of *chuifong tokwan*, a pharmaceutical compound manufactured in Asia and sold illegally in the United States as a "miracle herb." Some artists' paints contain a yellow pigment made from cadmium sulfide. Cadmium at one time was a leachable component of the alloy used in ice cube trays.

Who's at Risk

Background levels of cadmium in food, water, and ambient air are not a health concern for the general North American population. Typical dietary intake is about 30 micrograms of cadmium per day (30 µg/day), a rate roughly ten times lower than that required to cause critical renal effects. Acute cadmium toxicity is rare because very high levels are seldom encountered in the workplace today, and low doses are not acutely toxic. An acute oral dose of 50 µg/kilogram (kg) body weight (about 3500 µg in an adult) is considered the minimal amount capable of causing gastric irritation. Chronic exposures, however, can be a major concern because cadmium has a tendency to accumulate in the body.

Persons in the United States at greatest risk of cadmium exposure are 500,000 workers, including the following:

Alloy makers
Aluminum solder makers
Ammunition makers
Auto mechanics
Battery makers
Bearing makers
Braziers and solderers
Cable, trolley wire makers
Cadmium platers
Cadmium vapor lamp makers
Ceramics, pottery makers
Copper-cadmium alloy makers
Dental amalgam makers
Electric instrument makers
Electrical condenser makers
Electroplaters
Engravers
Glass makers
Incandescent lamp makers
Jewelers
Lithographers
Lithopone makers
Mining and refining workers
Paint makers
Paint sprayers
Pesticide makers
Pharmaceutical workers
Photoelectric cell makers
Pigment makers
Plastic products makers
Sculptors, metal
Smelterers
Solder makers
Textile printers
Welders, cadmium alloy and cadmium-plate

☐ **Workers in industries producing or using cadmium have the greatest potential for cadmium exposure; hobbyists such as jewelry fabricators and artists may also be at increased risk.**

☐ **Cigarette smoke may add to the body's cadmium burden.**

☐ **Cadmium absorption may be increased in nutritionally deficient persons.**

Hobbyists may also encounter cadmium in their pursuits. For example, cadmium is present in many gold and silver solders used in fabricating jewelry and in the metal dust produced in grinding or engraving cadmium-plated surfaces. The likelihood of cadmium inhalation is increased in poorly ventilated work areas, and cadmium ingestion is increased by eating and smoking in these areas.

Cadmium air levels are usually thousands of times greater in the workplace than in the general environment. For example, the permissible exposure limit (PEL) of cadmium fume or cadmium oxide in the workplace is 100 micrograms per cubic meter of air (100 $\mu g/m^3$), whereas concentrations of cadmium in ambient air rarely exceed 0.0025 $\mu g/m^3$ in nonindustrialized areas and 0.040 $\mu g/m^3$ in urban areas. The U.S. Environmental Protection Agency (EPA) has estimated that 24-hour, lifelong inhalation of air containing 1 $\mu g/m^3$ cadmium is associated with a lung cancer risk of, at most, 2 additional cases in 1000 persons exposed.

Each cigarette contains 2 μg of cadmium, with 50% absorbed from the lungs during active cigarette smoking. Persons who smoke one pack per day typically have cadmium blood and body burdens approximately twice as high as those of nonsmokers.

Nutritional factors affect the amount of cadmium absorbed. Persons with low calcium, protein, or iron reserves absorb cadmium more efficiently and may be at increased risk of developing toxicity. Age and gender may also play a role. Iron-deficient neonates absorb greater amounts of cadmium than iron-deficient adults; females absorb more than males. Iron deficiency, resulting in increased cadmium absorption, may have contributed to the high incidence of itai-itai disease in multiparous Japanese women.

Challenge

(1) Additional information for the case study: The patient maintains a jewelry fabricating and engraving area in her home basement where she uses abrasive grinders, engraving equipment, soldering tools, and various raw materials. She does not use a dust mask but does wear a face shield when operating the grinder. The work area is dusty, with only two small windows near the top of one wall capable of providing ventilation; there is no local or general mechanical exhaust system. She admits to smoking and eating in the work area. The patient and her husband also tend a small garden in the backyard in which they grow vegetables for the table. A nearby wastewater treatment plant provides free fertilizer, which her husband applies to the garden every few weeks. The garden is irrigated with water from a municipal well.

What are the potential sources of cadmium exposure for this patient?

(2) Why is the patient described in the case study at increased risk of cadmium toxicity?

(3) Is the patient's husband also at increased risk? Explain.

Biologic Fate

Respiratory absorption of cadmium in humans is estimated to be from 30% to 60% of an inhaled dose, depending on particle size. Only the smallest particles penetrate to the alveoli, the major site of absorption. As a result, cadmium particles in fumes and cigarette smoke, which are smaller, are more completely absorbed than most cadmium particles of industrial origin.

In humans, no more than 5% of ingested cadmium is absorbed from the gut into the blood or lymphatic fluid. Although some nutritional factors increase this absorption, zinc and chromium can decrease cadmium uptake. Absorption through the skin is not a significant route of cadmium entry.

☐ **Cadmium has no known beneficial function in the human body.**

☐ **Cadmium is transported in the blood bound to metallothionein.**

☐ **The greatest cadmium concentrations are found in the kidneys and the liver.**

☐ **Urinary cadmium excretion is slow; however, it constitutes the major mechanism of elimination. Cadmium biologic half-life may be up to 30 years.**

Once absorbed, cadmium is distributed by the blood. Lymphocytes synthesize metallothionein, a metal-binding protein, which concentrates cadmium three-thousandfold. Cadmium does not undergo metabolic conversion *in vivo*.

Cadmium is eliminated from the body primarily in urine. The rate of excretion is low, probably because cadmium remains tightly bound to metallothionein, which is almost completely reabsorbed from the glomerular filtrate. Because excretion is slow, cadmium accumulation can be significant. Whereas cadmium concentration in blood reflects recent exposure, urinary cadmium concentration more closely reflects total body burden. However, when renal damage from cadmium exposure occurs, the excretion rate increases sharply, and urinary cadmium levels no longer reflect body burden.

The total cadmium body burden at birth is less than 1 µg, which gradually increases with age to about 30 milligrams (mg). The highest cadmium concentration is found in the kidneys, especially the renal cortex, followed by the liver, pancreas, and adrenals. In the kidney, cadmium concentration steadily increases over time, then declines at 50 to 60 years of age. In the liver, however, cadmium concentration increases continuously with age. The kidneys and liver together total about 50% of the body accumulation in humans.

Both the liver and kidneys store cadmium as a metallothionein complex, which serves not only to transport cadmium but also acts as a defense mechanism against the toxicity of the unbound cadmium ion. Ironically, it is the cadmium-metallothionein complex that accumulates in the kidneys and is partially responsible for cadmium's toxic renal effects. Cadmium does not accumulate in bone, and the blood-brain barrier appears to limit its uptake into the central nervous system. The placenta acts only as a partial barrier to fetal exposure.

The biologic half-life of cadmium in the body is estimated to be 30 years. This long half-life is due to the body's inability to deal with increasing cadmium intake by homeostatic control mechanisms; humans do not have an effective cadmium elimination pathway. Cadmium has no known biologic function in humans, and bioaccumulation appears to be a byproduct of increasing industrialization. Any excessive accumulation in the body should be regarded as potentially toxic.

Challenge

(4) Could diet play a role in the condition of the patient described in the case study?

Physiologic Effects

The mechanisms of cadmium toxicity are not fully understood but may involve binding of the metal to key cellular sulfhydryl groups, competition with other metals (zinc and selenium) for inclusion in metalloenzymes, and competition with calcium for binding sites on regulatory proteins such as calmodulin. The route and extent of cadmium exposure will influence the presentation of toxic effects.

☐ **Cadmium primarily affects the kidneys and skeletal system.**

Renal Effects

Nephrotoxicity may be caused by either chronic inhalation or chronic ingestion of the metal. Data from human studies suggest a latency period of approximately 10 years before clinical onset of renal damage, depending on intensity of exposure. Proteinuria appears to be irreversible, and continued exposure can lead to progressive renal dysfunction.

☐ **Cadmium toxicity may cause both tubular and glomerular damage with resultant proteinuria.**

Typically the proximal renal tubules are affected, resulting in a Fanconi-like syndrome with urinary excretion of low molecular weight proteins such as β_2-microglobulin, lysozyme, and retinol-binding protein. Glucosuria, aminoaciduria, increased excretion of calcium and phosphate, and decreased renal concentrating capacity also occur. Disturbances in calcium and phosphorus metabolism may subsequently lead to formation of kidney stones and demineralization of bones.

Tubular proteinuria may be accompanied by glomerular dysfunction with increased urinary excretion of high molecular weight proteins such as albumin, transferrin, and immunoglobulin G (IgG). An increased renal excretion of enzymes may also occur.

Skeletal Effects

☐ **Bone changes appear to be secondary to renal tubular dysfunction.**

Bone lesions usually occur late in severe chronic cadmium poisoning and include pseudofractures and other effects of osteomalacia and osteoporosis. Pseudofractures are spontaneous fractures that follow the distribution of stress in normal skeleton or occur at sites where major arteries cross the bone and cause mechanical stress through pulsation. Such fractures may have contributed to the waddling gait seen in Japanese patients with itai-itai disease.

Skeletal effects appear to be secondary to increased urinary calcium and phosphorus losses. These effects are compounded by inhibition of renal hydroxylation of vitamin D, which eventually leads to a deficiency of its active form. Some investigators believe cadmium also exerts an inhibitory effect on calcium absorption from the gastrointestinal tract.

Respiratory Effects

☐ **Acute cadmium inhalation may mimic metal fume fever.**

☐ **Chronic cadmium inhalation may result in impairment of pulmonary function with a reduction in ventilatory capacity.**

Acute cadmium oxide inhalation exposure occurs rarely, but has been reported to cause chemical pneumonitis and metal fume fever (a transient and generally benign syndrome of fever, malaise, and chest tightness). Studies have associated chronic cadmium inhalation with pulmonary function impairment, notably mild emphysema and pulmonary fibrosis with reduced ventilatory capacity. However, study limitations, such as small sample size, lack of a suitable cohort, and failure to control for the confounding effects of cigarette smoking, have raised questions about these findings. In one study of workers making copper-cadmium alloy, the largest reductions in forced expiratory volume in 1 second (FEV_1), its ratio to forced vital capacity ($FEV_1/FVC\%$), and gas transfer were noted in those cadmium workers with the highest liver cadmium levels and the highest cumulative cadmium exposures. Pulmonary changes appear to occur after renal damage and are rarely seen today.

Carcinogenic Effects

☐ **Cadmium's carcinogenic effects have been demonstrated in experimental animals; evidence in humans is less conclusive.**

Inhalation of cadmium chloride and intratracheal instillation of high doses of cadmium sulfide are associated with an increased frequency of lung tumors in rats. Inhalation of various cadmium compounds did not produce increased incidence of lung tumors in hamsters or mice, however.

Epidemiologic studies of workers suggest a possible association between cadmium inhalation and the development of lung, prostatic, and testicular cancer. Many of these studies failed to control for smoking or exposure to other chemicals, however, and only small numbers of persons were evaluated. No clinical or experimental evidence indicates that ingesting cadmium in food or drinking water causes cancer. This is also true in Japan, where oral intake of cadmium tends to be high. Despite the uncertainty regarding the carcinogenicity of cadmium in humans, EPA and the International Agency for Research on Cancer have classified cadmium as a probable human carcinogen when inhaled.

Developmental Effects

No conclusive evidence of cadmium-induced teratogenicity in either experimental animals or humans has been reported. In a Swedish epidemiologic study of pregnant women exposed to high cadmium concentrations in the workplace, an increased incidence of infants with low birth weight was reported.

☐ **No evidence of teratogenic effects in cadmium-exposed humans has been reported.**

Other Effects

Chronic cadmium exposure has been reported to cause mild anemia, anosmia, yellowing of teeth, and, occasionally, liver damage. There is no conclusive evidence that cadmium alone causes hypertension. However, cadmium-induced renal dysfunction can eventually manifest in hypertension.

Challenge

(5) Could cadmium intoxication explain the problem list and initial laboratory findings for the patient described in the case study? Explain.

Clinical Evaluation

History and Physical Examination

☐ **Concomitant exposure to other heavy metals should be assessed.**

Detailed questioning about occupations and hobbies is the key to including chronic cadmium poisoning in the differential diagnosis. Inhalation exposure most often occurs among workers and hobbyists when cadmium fumes are produced by high-temperature processes such as welding, smelting, and soldering, and where cadmium dust results from grinding.

In the general population, ingestion of cadmium-contaminated food is more likely to occur than inhalation of cadmium particles. Today, acute cadmium ingestion is unlikely to be a clinically significant source of exposure in North America. Chronic ingestion, however, is still possible in certain populations, for example, children with pica who ingest contaminated soil.

Signs and Symptoms

Adverse effects of excessive cadmium exposure may include the following:

- Acute Exposure
  - Gastroenteritis (ingestion only)
  - Bronchitis (inhalation only)*
  - Interstitial pneumonitis (inhalation only)
  - Pulmonary edema (inhalation only)

- Chronic Exposure
  - Proteinuria
  - Osteomalacia (itai-itai disease)
  - Pulmonary fibrosis (inhalation only)*
  - Liver damage (rare)
  - Hypertension
  - Lung cancer*
  - Prostatic cancer*
  - Mild anemia
  - Yellow discoloration of front teeth near gum line
  - Anosmia

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* Evidence of human health effects is inconclusive

Acute Exposure

Most acute cadmium inhalation exposures involve initial symptoms and physical findings relating to the respiratory system. The first symptom, usually throat irritation, may not be severe enough to prompt the worker to leave the area. Symptoms, which may be delayed by hours or days, include pleuritic chest pain, dyspnea, cyanosis, fever, tachycardia, and nausea. Depending on the extent of exposure, noncardiogenic pulmonary edema may appear and progress to death.

In the past, acute cadmium intoxication occurred after ingestion of acidic foods or beverages stored in cadmium-plated containers, with symptoms of severe nausea, vomiting, salivation, abdominal cramps, and diarrhea. Acute renal failure, cardiopulmonary depression, and shock due to fluid loss have also occurred. In humans, single lethal oral doses of cadmium have ranged from 350 to 8900 mg. An ingestion of 150 grams (g) of cadmium chloride was reported to produce facial edema, vomiting, hypotension, metabolic acidosis, pulmonary edema, oliguria, respiratory arrest, and, finally, death after 30 hours.

☐ **Acute inhalation of cadmium may cause symptoms similar to those of metal fume fever.**

☐ **Acute oral ingestion results in severe gastroenteritis.**

Chronic Exposure

Effects of chronic cadmium exposure are dose-dependent. Low-level chronic exposure produces few early physical findings. Severe chronic exposure leads to manifestations of renal tubular dysfunction, especially in postmenopausal, multiparous females. This group typically has calcium and vitamin deficiencies that can increase the gastrointestinal absorption of cadmium. Other symptoms include low back pain and bone pain secondary to pseudo- and pathologic fractures. Chronic cadmium intoxication may also play a role in the development of hypertension, although the association is weak. Anosmia and yellow discoloration of teeth near the gum line may be noted.

☐ **Mild anemia and yellow discoloration of teeth may occur.**

☐ **Chronic exposure may result in back pain and renal dysfunction.**

Laboratory Evaluation

Initial laboratory evaluation should focus on the kidneys. Screening tests include measures of renal dysfunction such as BUN, serum and urinary creatinine, serum and urinary protein, and glucose. Complete blood count, liver function tests, and chest

X ray (if cadmium inhalation is suspected) should be performed. Specialized laboratory tests include direct measurement of cadmium levels and more sophisticated renal function tests.

Direct Biologic Indicators

☐ **The best screening and diagnostic test for chronic cadmium exposure is a 24-hour urinary cadmium level, normalized to creatinine excretion.**

Urine cadmium. With low to moderate chronic exposure, urinary cadmium reflects the total body burden. The average daily excretion of cadmium in persons with no known cadmium exposure is usually below 1 μg/L, or 1 μg/g creatinine, increasing with age and smoking. When all cadmium-binding sites in the kidney become saturated, however, renal dysfunction results and the direct relationship to body burden is lost. The amount of cadmium excreted then increases dramatically, reflecting recent exposure rather than total body burden. When urinary cadmium levels are less than 10 μg/g creatinine, renal dysfunction is considered unlikely.

Serum cadmium. Serum cadmium levels reflect recent exposure and generally are not useful for evaluating chronically exposed patients. Normal serum concentrations of cadmium in nonexposed persons range from 0.05 to 0.3 micrograms per deciliter (μg/dL). Occupationally exposed persons may have levels ranging from 1 to 10 μg/dL. A blood level of 5 μg/dL or higher is considered toxic.

Cadmium in hair. Studies of exposed workers have not found a quantitative relationship between hair cadmium levels and body burden. Because of the potential for sample contamination, hair levels are not reliable either as a predictor of toxicity or as an indicator of occupational exposure.

Indirect Biologic Indicators

☐ **Urinary metallothionein and β_2-microglobulin excretion can be correlated with long-term cadmium exposure.**

The tests that follow have been used to determine renal damage in persons exposed to high cadmium levels. They may have little relevance in evaluating persons exposed to lower environmental levels, however.

Urinary β_2-microglobulin. This low molecular weight protein is found in increased amounts in the urine of patients with long-term cadmium exposure and is considered a more sensitive indicator of cadmium exposure than total proteinuria. However, other renal diseases, such as chronic pyelonephritis, also cause increased β_2-microglobulin excretion. Excretion of β_2-microglobulin increases with age and cadmium exposure, but has been reported to average about 200 µg/g creatinine in unexposed persons.

Urinary metallothionein. Metallothionein is a low molecular weight protein synthesized in response to the presence of divalent metals such as cadmium, zinc, and copper. The protein is formed primarily in the lymphocytes, kidney, liver, and intestine. Its function appears to be the binding of metal ions, thus rendering them less toxic. Once metallothionein binds to cadmium, the complex preferentially accumulates in the kidney. Urinary levels of metallothionein correlate well with urinary cadmium levels and can reflect total cadmium body burden; however, urinary concentration of the cadmium-metallothionein complex increases significantly once renal dysfunction has developed.

Urinary retinol-binding protein. Retinol-binding protein is another low molecular weight protein appearing in the urine after chronic cadmium exposure. It is excreted when tubular reabsorption decreases due to any cause and, therefore, is nonspecific and can be used only as a supportive test in cases of suspected cadmium exposure.

Challenge

(6) If you suspect cadmium poisoning, what other questions could help gauge the extent of exposure to the patient described in the case study?

(7) What tests would be helpful in further evaluating the patient or in supporting a diagnosis of cadmium toxicity?

(8) Assuming the patient described in the case study has cadmium toxicity, what would be a likely urinary cadmium level?

Treatment and Management

One exposed person often signals potential or actual exposure of others, with the possibility of a common exposure source. Such sources include the workplace, drinking water supply, community irrigation, proximity to a smelter, and so on. Public health authorities should be notified whenever cadmium toxicity is suspected in a patient so that case-finding may be initiated and preventive measures taken.

Acute Exposure

☐ **There is no specific antidote for cadmium poisoning.**

There is no effective treatment for cadmium poisoning. Standard chelation therapy using ethylenediaminetetraacetic acid (EDTA), British anti-Lewisite (BAL or dimercaprol), or dimercaptosuccinic acid (DMSA) has generally not proven effective. BAL is contraindicated because it may increase nephrotoxicity. Treatment remains supportive, including fluid replacement, supplemental oxygen, and mechanical ventilation, if necessary. In cases of ingestion, gastric decontamination by emesis or gastric lavage may be beneficial soon after exposure. Administration of activated charcoal has not been proven effective.

Chronic Exposure

☐ **Prevention of further exposure is the most important step in management of patients with symptoms suggestive of cadmium intoxication.**

The mainstay of therapy in chronic poisoning involves removing the patient from further exposure. In the workplace, engineering controls, improved ventilation, and personal hygiene are the first line of defense. In addition, patient and worker education is vital in encouraging preventive behavior and in assisting early detection of cadmium toxicity. Respiratory protection should be worn in occupational or hobby settings where airborne concentrations may exceed allowable limits. Smoking, eating, and drinking in the work area should be discouraged.

Challenge

(9) What treatment will you recommend for the patient described in the case study?

(10) Should the patient's neighbors be evaluated for cadmium or other heavy-metal exposure? Explain.

Standards and Regulations

With increasing evidence of its toxicity, both national and international agencies have sought to regulate cadmium exposure. These efforts encompass workplace and environmental guidelines or regulations for air emissions, drinking water, food, industrial discharges, and hazardous waste concentrations. Table 1 summarizes standards, regulations, and guidelines for cadmium.

Table 1. Standards and regulations for cadmium

Agency*	Focus	Level	Comments
ACGIH	Air-Workplace		
	cadmium dust	0.05 mg/m^3	Advisory; TWA†
	cadmium fume	0.05 mg/m^3	15-minute ceiling limit
NIOSH	Air-Workplace	N/A	Advisory; lowest possible limit based on carcinogenic risk
OSHA	Air-Workplace		
	cadmium dust	0.2 mg/m^3	Regulation; PEL§
	cadmium fume	0.1 mg/m^3	
EPA	Air	N/A	Under review
	Water	0.01 ppm	Regulation; maximum contaminant level in drinking water; suggested revision to 0.005 ppm
WHO	Food	0.4-0.5 mg	Advisory; provisional tolerable weekly intake for adults

* ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; WHO = World Health Organization

† TWA (Time-Weighted Average) = time-weighted average concentration for a normal 8-hour workday and 40-hour workweek to which nearly all workers may be repeatedly exposed

§ PEL (Permissible Exposure Limit) = highest level averaged over a normal workday, to which a worker may be exposed

Workplace

Air

The PEL for airborne cadmium in the workplace has been set by the Occupational Safety and Health Administration (OSHA) at 0.2 mg/m^3 as an 8-hour time-weighted average (TWA) for cadmium dust, and 0.1 mg/m^3 for cadmium fume (cadmium oxide). A 15-minute ceiling concentration of 0.6 mg/m^3 for cadmium dust

☐ **OSHA has proposed lowering cadmium workplace exposures by 99%.**

and 0.3 mg/m^3 for cadmium fume (cadmium oxide) has been mandated. OSHA's proposed 1990 ruling seeks to reduce permissible cadmium workplace exposures by 99%.

The National Institute for Occupational Safety and Health (NIOSH) recommends that cadmium be regarded as a potential carcinogen based both on epidemiologic studies of lung cancer among workers and laboratory studies.

Environment

Air

☐ **No EPA air standard for cadmium currently exists.**

Cadmium levels in the ambient atmosphere are generally low. Typically, cadmium concentrations range from 1 to 5 nanograms per cubic meter (ng/m^3) in sparsely populated rural areas and from 5 to 40 ng/m^3 in urban air. In the vicinity of active zinc or lead smelters, cadmium values of 300 to 700 ng/m^3 have been measured at distances of 0.5 to 1 kilometer from the smelter. Near incinerators, average cadmium air levels have been estimated to be 7 ng/m^3. EPA is seeking classification of cadmium as a hazardous air pollutant; however, no ambient air standard for cadmium currently exists.

Water

☐ **EPA has proposed lowering the regulated level of cadmium in drinking water.**

EPA has established a maximum contaminant level (MCL) for cadmium in drinking water of 0.010 mg/L (0.01 ppm) and is currently seeking its revision to 0.005 mg/L (0.005 ppm). EPA and some states regulate the amount of cadmium discharged in industrial wastewaters.

Food

☐ **Dietary cadmium is not regulated.**

Average daily dietary cadmium intake is 10 to 50 µg. The World Health Organization has recommended a provisional tolerable weekly intake of 400 to 500 µg cadmium for adults. Nevertheless, the exact amount of cadmium in the average American diet is difficult to control. For this reason, efforts have been directed toward reducing cadmium discharged into waterways and deposited on soil, which could eventually enter the food chain.

Soil

☐ **EPA regulates application of solid waste to topsoil.**

A 1979 report noted that topsoils in the United States contain an average cadmium level of about 260 µg/kg. Levels in soil near sources of contamination may greatly exceed this value. Crops grown in contaminated soil are capable of translocating the metal and present a likelihood of exposure to consumers. Currently, there is no effective way to decontaminate soil. EPA regulation for application of solid waste to topsoil used in crop production for human consumption is 0.5 kg of solid waste per hectare annually.

Suggested Reading List

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Answers to Pretest and Challenge Questions

Pretest is found on page 1. Challenge questions begin on page 5.

(1) Potential sources of cadmium are as follows:
  (a) cadmium fume (cadmium oxide) generated by use of gold and silver solders during jewelry fabrication
  (b) cadmium dust produced in smoothing jewelry with abrasive grinding or in engraving cadmium-plated surfaces
  (c) food and cigarettes in the workplace contaminated by cadmium-containing particulates and dust
  (d) cigarette smoke
  (e) food grown in soil contaminated with cadmium-containing fertilizer obtained from the wastewater treatment plant

(2) Risk factors are due to not only increased opportunity for cadmium exposure, but age and nutritional status as well. The patient's hobby, jewelry fabrication, may provide low-to-moderate chronic cadmium exposure. Lack of respiratory protection, poor ventilation, and poor hygiene in the work area increase the amount of her exposure. The patient also inhales approximately 2 µg cadmium with each cigarette smoked. The amount of cadmium ingested from the vegetables grown in her garden is unknown, but sludges from wastewater treatment plants have been found to contain significant levels of cadmium. Factors that may enhance cadmium absorption from the gut are age and certain dietary deficiencies.

(3) Yes, the patient's husband also may be at increased risk of cadmium toxicity because of increased opportunity for exposure, although his risk is probably less than his wife's. The husband is exposed to cadmium by eating food from the contaminated garden and by inhaling tobacco smoke from cigarettes, even more so if he smokes. In the basement work area, he may encounter cadmium fumes and dust as a result of his wife's hobby. He also may be exposed to the cadmium on his wife's clothing and skin if she does not shower and change clothes before leaving the work area.

(4) Yes, diet could play an important role in the patient's condition, both for what it contributes and for what it does not include. For example, the homegrown vegetables from the garden, particularly leafy vegetables, and animal liver or kidney and shellfish could be contributing to her cadmium burden. If her diet is deficient in iron, calcium, or protein she may be absorbing cadmium more efficiently.

(5) The patient's problem list includes the following:
  back pain
  severe osteomalacia and mild osteoporosis
  pseudofractures
  yellow discoloration of the teeth
  proteinuria and glycosuria

All of these are consistent with chronic cadmium toxicity. The patient is also a smoker. Chronic cadmium exposure primarily affects the kidneys and skeleton. Renal dysfunction in this patient is indicated by the laboratory findings. The stooped posture, waddling gait, lumbar pain, and pain induced by spinal percussion are the result of skeletal changes and deformities.

(6) Most of your questions will probably center on the patient's hobby, as this is the greatest potential source of cadmium exposure. Typical questions would include the following:
   (a) What types of materials and metals are used in making jewelry? What are the ingredients of all composite products?
   (b) On a weekly basis, how many hours are spent fabricating jewelry in the basement?
   (c) What type of face shield is used? Why is respiratory protection not used during grinding and soldering operations?
   (d) Is the work area kept clean and free of dust? How?
   (e) Does she wash her hands before eating in the work area and are attempts made to keep food and cigarettes from becoming contaminated by dust and particulates?
   (f) Does she shower and change her clothes before leaving the work area?

It is also important to investigate smoking habits.

(7) The most useful diagnostic test for cadmium exposure is a 24-hour urinary cadmium excretion standardized for creatinine. β_2-microglobulin levels, in conjunction with cadmium excretion, will aid in evaluating subclinical renal dysfunction. The following tests also may be helpful in evaluating the patient: urinary protein and glucose, LDH, SGPT or ALT, and SGOT or AST. A chest X ray and pulmonary function test should be obtained if cadmium inhalation is a factor.

(8) The patient is experiencing renal dysfunction, as evidenced by the 3^+ level of proteinuria and glycosuria. When proximal tubular damage occurs, cadmium excretion can result from two sources; breakdown of the tubular epithelium and decreased reabsorption. Under these conditions, urinary cadmium levels are likely to be markedly increased and no longer reflect body burden. Exposed workers can excrete several hundred micrograms of cadmium per gram of creatinine; urinary cadmium levels in an unexposed population are typically between 1 and 10 µg cadmium/g creatinine. The patient therefore would be expected to have a urinary cadmium level of several hundred micrograms of cadmium per gram of creatinine, depending on her most recent exposure.

(9) There is no effective treatment for cadmium toxicity; chelation therapy has no role in cadmium poisoning. Removal from the source of exposure and patient education to significantly reduce exposure are important, particularly before the condition has progressed to irreversible renal dysfunction. Supportive measures to alleviate symptoms should be provided.

10) The neighbors should be evaluated and educated. Even if they do not use the fertilizer from the wastewater treatment plant or water from the same irrigation source, runoff from the patient's land may contaminate their soil or well water. Consultation with the local or state health department is advisable if a potential public health hazard exists.

CASE REPORT

Jeff R. Farrow,[1] *M.D.; Gregory J. Davis,*[2] *M.D.; Thomas M. Roy,*[1] *M.D., F.C.C.P.; L. C. McCloud,*[2] *M.D.; and George R. Nichols II,*[2] *M.D.*

Fetal Death Due to Nonlethal Maternal Carbon Monoxide Poisoning

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REFERENCE: Farrow, J. R., Davis, G. J., Roy, T. M., McCloud, L. C., and Nichols, G. R. II, **"Fetal Death Due to Nonlethal Maternal Carbon Monoxide Poisoning,"** *Journal of Forensic Sciences*, JFSCA, Vol. 35, No. 6, Nov. 1990, pp. 1448–1452.

ABSTRACT: Fetal death due to acute carbon monoxide poisoning is rarely reported in the medical literature. Of the eight cases found in literature review, only one documented the fetal carboxyhemoglobin concentration. This paper reports a fetal death due to accidental nonlethal maternal carbon monoxide intoxication in which both maternal and fetal carboxyhemoglobin concentrations were obtained. The corrected carboxyhemoglobin concentration was 61% at the time of death in utero, while the maternal carboxyhemoglobin was measured at 7% after one hour of supplemental oxygen. The authors review the mechanisms of fetal death and emphasize the different carbon monoxide kinetics in the fetal circulation.

KEYWORDS: toxicology, carbon monoxide, fetal death

Carbon monoxide (CO), the gas produced by the incomplete combustion of carbon-containing materials, is the leading cause of poison-induced deaths in the United States [*1*]. This environmental hazard is ubiquitous and, in homes, is usually produced in toxic concentrations by faulty heating units which are poorly ventilated [*2*]. Approximately 3500 to 4000 deaths each year are attributed to carbon monoxide intoxication in the United States [*1*]. Fetal death due to maternal CO poisoning has only rarely been reported. Of the eight cases published in the English-language medical literature, only one report provides the carboxyhemoglobin (COHb) concentrations of both the mother and the fetus [*3*]. We present the circumstances of another fetal death due to a nonlethal maternal CO poisoning in which COHb levels were obtained for both mother and fetus. Documentation of the COHb levels provides us with an opportunity to emphasize the

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difference in CO kinetics between the mother and the fetus and to call attention to the current recommendations for treating this medical emergency when a pregnant female is involved.

Case Report

A 20-year-old white female arrived by ambulance at the hospital approximately 60 min after being found unconscious at her mobile home. She had been intubated by the Emergency Medical Services and had received 100% supplemental oxygen en route to the hospital. The patient's 21-year-old husband was also found at the scene and brought to the hospital. Although initially disoriented, restless, and combative, he was lucid at the time of arrival in the emergency department. From his history, it was determined that the couple's usual heater was in disrepair, and a portable propane heater was the sole source of heat in their unventilated mobile home. He also disclosed that his wife was 28 weeks into her first pregnancy, that her past medical history was unremarkable, and that she was not currently taking medications or using cigarettes.

During the initial physical examination, the patient was noted to be combative and confused. Her blood pressure was palpable by cuff measurement at 80 torr systolic. She was being ventilated by a volume-cycled ventilator which she triggered 26 times a minute. Carbonaceous material was found in the nares, oropharynx, and adherent to the endotracheal tube. No burns of the skin, nasal hair, face, or eyebrows were present. Abdominal examination results were consistent with a 28-week intrauterine pregnancy.

No fetal movement could be detected by ultrasound, and fetal heart sounds were absent. Peripheral cyanosis was noted in her nail beds. The measured carboxyhemoglobin concentration at the time of admission was 7%. A plasma and urine toxicology screen was negative. The initial chest radiograph was interpreted as showing bilateral alveolar infiltrates consistent with the adult respiratory distress syndrome.

On the second hospital day, the patient went into labor spontaneously and delivered a 1050-g stillborn female fetus of approximately 7 months gestation, with a crown-heel length of 39 cm and crown-rump length of 27 cm. The gross autopsy findings were remarkable only for bright red discoloration of the skin and visceral organs. The corrected fetal COHb saturation at the time of the autopsy was 61% by IL 282-CO-Oximeter[1] [*4*]. On microscopic examination of the tissues, the expected autolytic changes were seen but no other diagnostic abnormalities were found.

The mother began a slow convalescence after delivery of the fetus and subsequently recovered normal pulmonary function. She was discharged on the ninth hospital day.

Discussion

Approximately 3500 to 4000 deaths each year in the United States are caused from carbon monoxide (CO), the nonirritating, odorless, tasteless, and colorless inert gas that is produced by the incomplete combustion of carbon-containing materials [*1*].

CO has an affinity for reversibly binding with adult hemoglobin that is 250 times greater than that of oxygen [*5*]. Measurement of the carboxyhemoglobin (COHb) level provides the clinician with an objective parameter to correlate with clinical symptoms and prognosis. Because CO is endogenously produced in humans during metabolism of protoporphyrin to bilirubin during hemoglobin metabolism, a nonsmoking individual may have a normal resting COHb saturation of 1 to 3% [*6*]. Cigarette smokers will commonly have

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[1] The IL 282 CO-Oximeter is manufactured by Instrumentation Laboratory, Inc., Lexington, MA 02173.

COHb levels of 5 to 6%, and, if they smoke continuously, COHb levels may reach 8 to 10% [7].

CO interferes with cellular metabolism by inhibiting the transport, delivery, and utilization of oxygen. CO successfully competes for oxygen binding sites. The hemoglobin molecule will then bind more avidly to the oxygen molecules on its surface, resulting in a shift of the oxyhemoglobin dissociation curve to the left. Finally, CO poisons cellular respiration by displacing oxygen from receptors of the cytochrome oxidase system, particularly cytochrome a3 and cytochrome P-450 [6].

In adults, COHb concentrations of 30 to 40% are generally associated with weakness, dizziness, nausea and vomiting, and cardiovascular collapse. Syncope, seizures, and death may occur with COHb levels of 50% [8]. Inhalation of ambient gas which has a CO concentration of 1% can be fatal within 10 min, depending on the victim's activity and respiratory rate [9]. Likewise, victims with underlying diseases such as anemia, heart dysfunction, or lung disease may succumb at much lower COHb concentrations [7].

Interestingly, Goldbaum [10] has shown that CO is toxic only when inhaled through the lungs and not when introduced by intraperitoneal injection or transfusion with CO-saturated red cells. He asserts that the toxic effects of CO are not caused by elevated COHb alone, such as occurs in the latter two instances, but also by direct action of dissolved CO on the cytochrome oxidase system. Thus, he cautions that COHb determination may be misleading without knowledge of environmental conditions and the respiratory status of the individuals affected.

Investigations of CO exchange between mother and fetus have shown that CO absorption and elimination occur more slowly in the fetal circulation [11,12]. Following maternal exposure to CO, the fetal COHb rises more slowly than the maternal COHb but will continue to rise for several hours after acute exposure until it eventually reaches an equilibrium at a level which is approximately 10% greater than the mother's COHb saturation [12]. The pattern of elimination of CO is similar, and fetal COHb concentrations diminish more slowly than maternal COHb levels [13]. Although there is some evidence that the placenta has some capacity to transport CO actively, passive diffusion through the placenta along a partial pressure gradient is thought to account for the bulk of fetal CO absorption and elimination [14].

Our case further illustrates the differing CO kinetics between the maternal and fetal circulations. The normal COHb half-life of 4 to 5 h when breathing room air with an oxygen concentration of approximately 21%, can be markedly shortened by inhaling oxygen at higher concentrations. If 100% supplemental oxygen is administered, the COHb half-life is shortened to 60 min [8]. Approximately 40 to 50% of the body's CO can be eliminated in 1 h when high fractions of oxygen are rapidly administered by emergency rescue teams [7]. Unfortunately, it is estimated that it takes four to five times as long for the fetal COHb to decrease to the same maternal COHb level [14]. The implications for treatment of the pregnant victim are clear.

Fetal tissues are at greater risk from hypoxia caused by CO since a higher COHb equilibrium is achieved, COHb elimination is delayed, and the fetal hemoglobin experiences a more accentuated left shift than does adult hemoglobin [15]. This particular susceptibility of fetal tissue to CO toxicity has promoted interest in utilizing hyperbaric oxygen for the treatment of the pregnant patient with CO poisoning. With the use of 100% oxygen at 2 to 3 atmospheres of pressure, the COHb elimination can be significantly enhanced in both mother and fetus [14]. In lieu of this modality, supplemental oxygen at concentrations approaching 100% should be administered for five times the length of time needed to reduce the maternal COHb to acceptable concentrations [14].

The mother in our report is assumed to have reached a minimal COHb concentration of 40 to 50% since she sustained loss of consciousness. Therefore, with the kinetics described, the fetus would be expected to develop a COHb level of at least 65%. To explain the disparity between maternal and fetal COHb concentrations in our case, it is necessary to postulate that fetal death occurred at the time that the fetal circulation reached its maximal COHb saturation. According to available research information, the fetal COHb concentration is not expected to change after death in utero. CO is not produced by decomposition, nor is it absorbed in significant amounts by a body when exposed to an environment rich in CO. Indeed, COHb persists for weeks in the human body and may be accurately quantified even after embalming and burial [7].

In chronic or nonfatal CO poisoning, degenerative changes can often be seen involving the basal ganglia, kidneys, liver, and heart. These lesions are indicative of severe tissue hypoxia and are not pathognomonic of CO poisoning [9]. In acute asphyxia due to CO, death occurs before these lesions can develop. The fetal autopsy suggested COHb poisoning by the cherry red discoloration of the skin and visceral organs.

The carboxyhemoglobin concentration that causes fetal death in humans has not yet been defined. The clinician's ability to predict fetal survival is poor because the fetal COHb concentration cannot be estimated from a single determination of maternal concentration without knowledge of the maternal exposure pattern. At the present time, the best predictive index of fetal morbidity and mortality appears to be the severity of maternal symptoms at the site of exposure.

The authors hope that this account of fetal death associated with nonfatal maternal exposure to CO, which is only the second report to include measurement of both maternal and fetal COHb saturations, will alert both death investigators and clinicians to the fragile relationship that exists between mother and fetus under circumstances of CO exposure.

Addendum

Since the completion of this report, an additional recent case of nonlethal maternal CO poisoning with fetal death has come to the authors' attention.[4]

Acknowledgment

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ATSDR September 1992
Case Studies in Environmental Medicine

18

Carbon Tetrachloride Toxicity

Environmental ALERT . . .

☑ *Carbon tetrachloride (CCl_4) is regarded as highly toxic. It is a known animal carcinogen and a potential human carcinogen.*

☑ *CCl_4 has become a model for the study of agents that cause localized cellular injury via a free-radical mechanism.*

☑ *Because CCl_4 is chemically stable, it has a long atmospheric half-life. Very little CCl_4 is released to the environment via water; what is released to surface waters rapidly volatilizes.*

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. See page 18 for more information about continuing medical education credits and continuing education units.

Guest Contributor: Lora E. Fleming, MD, MPH, MSc
Guest Editor: Michael Hodgson, MD

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

A hazardous waste worker with delayed onset abdominal pain, nausea, vomiting, and diarrhea

As the physician on duty at a hospital emergency department (ED) in an urban community, you are notified that three hazardous waste workers—two men and a woman—are being transported from their worksite by ambulance. All three workers are complaining of headache, dizziness, and nausea.

You learn that the workers were handling several dozen barrels of a sweet-smelling hazardous waste liquid in a hot, unventilated room. Their work required taking samples from barrels, which were obtained from a defunct chlorofluorocarbon manufacturing plant. All three workers were initially wearing full-face respirators and protective clothing, but the younger man removed his respirator early in the day because he had a hangover and was nauseated; he felt it was more convenient to work without being hampered by the respirator. The other two workers continued in full protective gear. After 3 to 4 hours, the three workers began to experience symptoms.

Physical examinations of the workers are conducted in the ED. The older man's and woman's results are normal. Their symptoms subside within 2 hours, and they are discharged.

The younger man, however, has trouble concentrating and is mildly ataxic. His initial blood laboratory data are within normal limits, but he is kept under close observation. You learn from the young man that he is aged 25 and has been in good health with no history of similar problems. Last night, in celebration of his birthday, uncharacteristically he drank 9 to 12 beers, which accounts for his hangover this morning. He also mentions that this morning, while cleaning several wounds sustained in a fight the prior evening, he spilled a can of isopropyl alcohol on his hands and clothes but did not bother to change his clothing.

Six hours later, while still in the ED, the young man becomes acutely ill. He has abdominal pain, nausea, vomiting, and diarrhea. His rectal temperature is now 101°F, pulse 140/min, and he has become disoriented and drowsy. Two days after hospital admission he still has an elevated temperature and abnormal laboratory tests as follows: serum creatinine 2.0 mg/dL (normal 0.7 to 1.5); SGOT or AST 80 U/L (normal 7 to 45); total bilirubin 2.4 mg/dL (normal 0.1 to 1.4); PT 15 seconds (normal 10 to 13). Urinalysis reveals 2^+ proteinurea, and urine output has decreased despite intravenous hydration.

Pretest

(a) *What is the possible clinical course for this young man?*

(b) *How will you identify the material to which the workers have been exposed?*

(c) *What treatment or antidote would you consider for the patient?*

Answers to pretest questions may be found on page 15.

Exposure Pathways

- ☐ **In the United States, most industrial CCl_4 is used in the synthesis of CFCs and chlorinated solvents. Production and usage is declining.**
- ☐ **Sources of environmental contamination include industrial and hazardous waste sites.**

Carbon tetrachloride (CCl_4) is a clear, nonflammable, heavy liquid that evaporates readily, producing a sweet odor. Although CCl_4 does not occur naturally, it is ubiquitous in the environment. Its chemical stability results in an atmospheric half-life of 30 to 100 years. While CCl_4 does not photodegrade in the ambient air, it may degrade in the presence of the shorter ultraviolet radiation found in the stratosphere. Synonyms for carbon tetrachloride include *tetrachloromethane*, *carbon tet*, *carbona*, *tetrasol*, and *carbon chloride*.

Acute CCl_4 toxicity in the workplace was widely recognized by the 1950s. Since then, CCl_4 manufacture and use have decreased. Today, most CCl_4 is consumed in the synthesis of chlorofluorocarbons (CFCs), which are used as heat transfer agents in refrigerating equipment and as aerosol propellents. Because of recent international agreements to restrict the use of CFCs, which are thought to deplete the earth's protective ozone layer, production of CCl_4 will most likely continue to decline. Minor amounts of CCl_4 are still used as an industrial solvent for oils, fats, lacquers, pesticides, varnishes, rubber, waxes, and resins. The largest source of CCl_4 release has been from the fumigation of grains and other substances. In 1986, CCl_4 fumigation was banned except for preserving museum artifacts.

In the United States, CCl_4 has been used widely as an industrial and household cleaning fluid. In industry, it was an effective metal-degreaser, and in the home, it was used to remove spots from clothing, furniture, and carpets. CCl_4 also has been used as an extracting solvent for flowers and seeds, as a component in fire extinguishers, as an anthelmintic and anesthetic, and until 1969, as a waterless shampoo. CCl_4 is still used for many of these purposes in Europe and the third world.

The general population may be exposed to small amounts of CCl_4 through ambient air. Sources producing concentrations that are above background levels include industrial locations where CCl_4 is still used and chemical waste sites where emissions into air, water, or soil are not controlled properly. In 1983, the average atmospheric background level in rural areas was 0.13 parts per billion (ppb); average levels in suburban and urban areas were 0.19 ppb. The Environmental Protection Agency (EPA) has estimated that a lifetime exposure to 0.11 ppb CCl_4 in air causes an excess risk of, at most, one additional cancer in a population of 100,000 people exposed. Before 1988, global atmospheric levels of CCl_4 steadily increased by about 1.3% per year, but they will most likely decline in the future due to decreasing CCl_4

production. Concentrations indoors are often higher than outdoors, indicating that building materials or products such as pesticides and cleaning agents inside the home may be a source of airborne CCl_4.

Because of its moderate solubility in water and its relatively high rate of volatilization from water, only about 1% of the total CCl_4 found in the environment is dissolved in surface waters and oceans. The results of surveys performed by the federal government show that about 99% of all groundwater supplies and about 95% of all surface water supplies contain less than 0.5 ppb of CCl_4. The EPA maximum contaminant level (MCL) for drinking water is 5 ppb.

Who's at Risk

Workers employed in industries that manufacture or use CCl_4 are at greatest risk of exposure. According to a 1981–1983 survey, about 58,000 workers are exposed to CCl_4 in the United States; however, phase-out of the solvent will most likely decrease the number of exposures. Although inhaled CCl_4 has been associated with liver and kidney damage, exposure at current permissible airborne levels in the workplace is not linked to chronic disease. Workers who may be exposed to CCl_4 include the following:

air transportation workers
automobile mechanics*
dry cleaners*
grain workers (inspection, storage, milling, processing)*
hazardous waste workers
museum workers
pesticide applicators*
pharmaceutical manufacturers
steel mill and blast furnace workers
telephone and telegraph equipment manufacturers
workers in tin-waste recovery operations

* CCl_4 is no longer used for this purpose in the United States.

People living near chemical plants where fugitive emissions of CCl_4 occur may be exposed to elevated levels of this chlorocarbon. Other populations at risk of exposure to CCl_4 include people living near chemical waste sites where CCl_4 is improperly stored.

The toxic metabolites of CCl_4 are produced from reactions mediated by mixed function oxidase (MFO) enzymes occurring primarily in the liver and kidneys; therefore, persons with increased MFO enzyme activity may produce toxic CCl_4 metabolites at a faster rate and may be more susceptible to CCl_4-induced effects. These include persons taking certain medications (such as barbiturates), and persons exposed to chlorinated insecticides (such as DDT, chlordecone, or mirex) or halogenated industrial chemicals (such as polychlorinated biphenyls). Triamcinolone and progesterone may also potentiate the effects of relatively moderate CCl_4 exposure.

☐ **Workers using CCl_4 or CCl_4-containing products are at greatest risk of exposure.**

☐ **Few cases of CCl_4 toxicity have occurred since the institution of industrial standards.**

☐ **Moderate to heavy drinkers and diabetics may be at increased risk of CCl_4's adverse effects.**

BEST COPY AVAILABLE

Alcohols (methanol, ethanol, and isopropyl alcohol) and their ketone analogues are known MFO inducers; hence, persons with a history of moderate or heavy ethanol abuse and those with poorly controlled diabetes may be at increased risk of CCl_4's harmful effects. Even in nonhabitual drinkers, ethanol intake up to 12 hours before CCl_4 exposure increases risk. Most occupational fatalities due to CCl_4 inhalation involve alcohol abusers; fatal toxicity rarely occurs in nondrinking patients.

Animal studies have demonstrated that fasting or consuming diets low in antioxidants (such as vitamin E, selenium, or methionine) can lead to increased hepatotoxicity from CCl_4 exposure although this effect has not been proven in humans. Persons with preexisting hepatic necrosis or cirrhosis or underlying renal disease appear to have increased susceptibility to CCl_4-induced toxicity and are at increased risk of subsequent liver cancer.

Although CCl_4 is not toxic to the fetus in most animal models, results of studies indicate that the human fetal MFO enzyme system may be operational in the later stages of development and can be induced by certain maternal exposures (e.g., cigarette smoke). Therefore, susceptibility of the human fetus to adverse effects of CCl_4 may depend on developmental stage and on duration and concentration of exposure.

Challenge

Information for the case study: You discuss the acute exposures with the workers' company supervisor. He suspects that the waste barrels contain CCl_4 since that chemical is a starting material in the synthesis of chlorofluorocarbons, and it has a sweet odor. The older male worker in the case study is aged 40, has a full beard, and has a history of alcoholism, although he has been abstinent for several years. He also has a history of hepatitis B due to a blood transfusion more than 10 years ago.

(1) If the material in the barrels is CCl_4, is this worker at increased risk?

(2) The female coworker later discovers she was almost 6 weeks pregnant at the time of this episode. Her obstetrician calls you to discuss the implications of the exposure to the fetus. What is your recommendation? Explain.

Biologic Fate

CCl_4 readily enters the body by inhalation, ingestion, and dermal absorption. Inhalation is the primary route of exposure, with pulmonary absorption in humans estimated to be 60%. The rate of absorption through the gastrointestinal tract is rapid and greatly affected by diet (e.g., fat or alcohol in the gut enhances CCl_4 absorption). CCl_4 also is absorbed through the skin, though less readily than by the lungs. Dermally, the liquid is more rapidly absorbed than the vapor, and prolonged skin contact with the liquid can result in systemic effects.

Few quantitative studies of CCl_4 absorption and distribution in humans have been reported. In experimental animals, CCl_4 is dispersed to all organs and tissues proportionate to blood perfusion and lipid content; the brain has the highest levels after inhalation or oral administration. The rate of inhalation absorption in humans decreases as the duration of exposure or dose increases, indicating a saturable metabolic pathway.

In humans, approximately 50% to 80% of a dose absorbed by the lungs is exhaled unchanged. Some CCl_4 temporarily enters fat tissue. After exposure ceases, CCl_4 continues to emerge from fat and is removed by the lungs. About 4% of all metabolized CCl_4 is converted directly to CO_2 and is exhaled; the remainder forms adducts with proteins and other cellular molecules. The adducts are degraded (half-life about 24 hours) and their products excreted mainly in urine and feces.

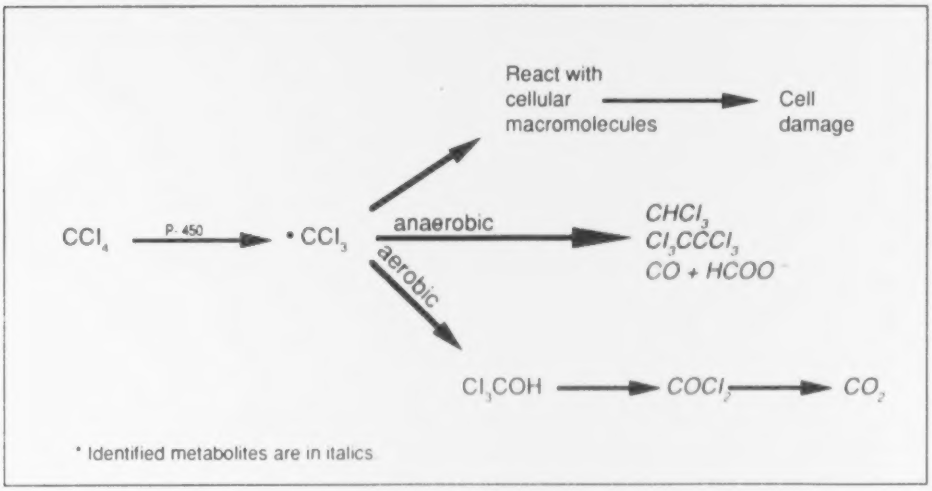
Bioactivation of CCl_4 has become the model for chemical toxicity induced by free radicals—a mechanism of toxic injury similar to that associated with radiation and the aging process. The results of studies with experimental animals indicate that the first step in CCl_4 metabolism may involve the formation of a trichloromethyl free radical ($\cdot CCl_3$) via the cytochrome P-450 enzyme system (Figure 1). The $\cdot CCl_3$ radical is postulated to bind directly to microsomal lipids and other cellular macromolecules, contributing to the breakdown of membrane structure and disrupting cell energy processes and protein synthesis. The $\cdot CCl_3$ radical also may undergo anaerobic reactions, resulting in the formation of a variety of toxins including chloroform ($CHCl_3$), hexachloroethane (Cl_3CCCl_3), and carbon monoxide (CO). In aerobic metabolism, the $\cdot CCl_3$ radical can yield trichloromethanol (Cl_3COH), a precursor to phosgene ($COCl_2$), which is then hydrolyzed to form CO_2.

☐ **CCl_4 is absorbed readily by all exposure routes.**

☐ **Evidence indicates that CCl_4 metabolism occurs via a free-radical intermediate.**

☐ **Elimination of CCl_4 occurs in two phases. Some inhaled CCl_4 is rapidly exhaled unchanged. A small amount of inhaled CCl_4 temporarily enters fat tissue and later emerges and is excreted.**

Figure 1. Products of CCl_4 metabolism*


CCl_4
P-450
$\cdot CCl_3$
React with cellular macromolecules
Cell damage
anaerobic
$CHCl_3$
Cl_3CCCl_3
$CO + HCOO^-$
aerobic
Cl_3COH
$COCl_2$
CO_2

* Identified metabolites are in italics

Physiologic Effects

The immediate effect of acute CCl_4 exposure by all routes is central nervous system (CNS) depression. If the patient survives this immediate effect, death is usually due to hepatic or renal injury. Adverse effects to other organs are likely to be secondary to CNS, liver, or kidney damage. CCl_4 is classified as a potential human carcinogen based on results of studies that indicate ingested CCl_4 increases the frequency of liver tumors in experimental animals.

Neurologic Effects

☐ **Acute exposure to CCl_4 may lead to rapid CNS depression.**

CCl_4 rapidly produces a narcotic effect on the brain. Immediate fatalities result either from respiratory depression (due to direct CNS effects) or from cardiac dysrhythmias. In severe cases, autopsy reveals permanent damage to nerve cells with focal areas of fatty degeneration and demyelination, Purkinje cell damage, and patchy pontine necrosis. Inhalation exposure can result in acute cerebellar dysfunction.

Hepatic and Renal Effects

Carbon tetrachloride is a well-known hepatotoxic agent. In acute lethal CCl_4 exposures, autopsy reveals marked hepatic steatosis (fatty degeneration) and centrilobar necrosis. The toxic metabolites of CCl_4 block formation and release of low-density lipoproteins and deplete hepatic stores of glutathione. Centrilobular necrosis possibly results from reactions of initial free-radical intermediates. (See *Biologic Fate*, page 5.) In addition, a dramatic increase in calcium concentration occurs in hepatic mitochondria, accompanied by alterations in electrolyte distribution with swelling of hepatic cells and depletion of liver glycogen.

- ☐ **Hepatic and renal toxicity are due to biotransformation of CCl_4 to toxic metabolites.**
- ☐ **CCl_4 toxicity is potentiated by chemicals that activate the cytochrome P-450 system.**

Hepatic injury, which usually manifests after CNS effects have subsided, typically occurs 1 to 4 days after acute exposure. Jaundice develops in about 50% of poisoning cases and typically evolves rapidly. Recovery from acute exposure is usually complete, with no long-term sequelae. Chronic exposure may result in fibrosis or cirrhosis. A decrease in clotting factors (due to acute liver damage) may predispose the patient to hemorrhage.

Exposure to CCl_4 can result in nephritis, nephrosis, and renal failure. Within hours after manifestation of hepatic damage, renal failure may begin and typically reaches a peak in the second week after exposure. Oliguria or anuria may develop by the second to fourth day after exposure with concomitant edema, azotemia, proteinuria, hemoglobinuria, and glucosuria. Hypertension and acidosis may develop. Occasional moderate elevations in white cell counts occur, possibly in response to necrotic liver or kidney injury.

Fluid overload can lead to pulmonary congestion and edema. CCl_4 also may have direct toxic effects on the lungs. Changes in blood pressure or heart rate are probably secondary to renal effects on fluid and electrolyte retention or to CNS effects on the heart or blood vessels. Kidney failure is the main cause of death in many patients with acute CCl_4 exposure.

Carcinogenic Effects

Although data on the carcinogenic effects in humans are inconclusive, studies in experimental animals provide convincing evidence that ingestion of CCl_4 increases the risk of liver cancer, in particular, hepatomas and hepatocellular carcinomas. It is speculated that highly reactive metabolic free radicals combine with hepatic macromolecules to cause these effects. The National Institute for Occupational Safety and Health (NIOSH) has identified CCl_4 as a potential human carcinogen. The American Conference of Governmental Industrial Hygienists (ACGIH) considers CCl_4 a suspected human carcinogen.

Challenge

Additional information for the case study: Early that evening, the manager calls to inform you that the company has identified the hazardous waste as CCl_4.

(3) Knowing the exposure was to CCl_4, do you consider the patient to be at increased risk of acute health effects? Why?

Clinical Evaluation

No unique pattern characterizes acute or chronic CCl_4-induced illness. Diagnosis is based on a history of exposure and the clinical signs including CNS depression, dysrhythmias, and hepatic necrosis.

History and Physical Examination

- ☐ **The occupational and environmental history is essential to diagnosing CCl_4 toxicity.**
- ☐ **The physical examination should focus on the neurologic and gastrointestinal systems.**

The patient's occupational history is crucial. For each job held, the history should include the name and location of the company, job title, description of chemical processes employed, known toxic agents, and history of worker illness. Additional helpful information includes history of exposure to other known hepatotoxic agents (e.g., medications and ethanol), history of hepatic and renal disease, and an environmental history including type of water supply, location and duration of residence, proximity to industry, and patient's hobbies.

In acute exposure, the initial physical examination should concentrate on the neurologic system. One to six days after an acute exposure, a patient may develop severe hepatic necrosis and renal failure, which can affect the cardiovascular and pulmonary systems. Toxic hepatitis, necrosis, and cirrhosis have been reported after chronic exposure to high levels of CCl_4.

Signs and Symptoms

Patients exposed to CCl_4 by any route exhibit predominantly CNS depression. Common symptoms, which are dose-dependent, include headache, giddiness, weakness, ataxia, lethargy, stupor, and coma. Complaints of restricted peripheral vision have been reported. In less severe cases, effects usually disappear within a day or two after exposure is stopped. Persistence of neurologic symptoms beyond 24 hours is more common when severe hepatic and renal damage also have occurred.

☐ **Regardless of CCl_4 exposure route, CNS effects predominate initially; symptoms of hepatic and renal damage may manifest later.**

Gastrointestinal symptoms of nausea, abdominal pain, vomiting, and diarrhea after acute exposure appear to be related to initial effects on the autonomic nervous system. Symptoms persisting beyond 24 hours may be the result of hepatic and renal injury. Signs may include hepatomegaly (right upper-quadrant pain), jaundice, oliguria, and anuria. Patients with hepatic and renal injury should be monitored for secondary signs of cardiac dysrythmias, pulmonary edema, and bleeding disorders.

Symptoms from chronic CCl_4 exposure are similar to those from acute exposure. Workers chronically exposed to CCl_4 have complained of headache, decreased peripheral vision, inability to think clearly, and dizziness; visual effects have been evaluated in many clinical studies without conclusive results. Persistent nausea should prompt an evaluation of the liver for toxic hepatitis.

Laboratory Tests

Direct Biologic Indicators

Carbon tetrachloride can be detected by gas chromatography in blood, serum, and adipose tissue, as well as other biologic and environmental materials. Even though refrigeration of blood samples in sealed tubes conserves the CCl_4 level, analysis should be performed within 24 hours. Any detectable blood level indicates exposure, although detectable levels are not necessarily indicative of adverse health effects. CCl_4 and other chlorinated hydrocarbons are radiopaque and may appear on abdominal X ray.

☐ **Any detectable amount of CCl_4 in the blood indicates exposure, although not necessarily adverse effects.**

Indirect Biologic Indicators

For persons exposed to CCl_4, baseline liver function tests (including SGOT [AST], SGPT [ALT], alkaline phosphatase, and bilirubin) and liver injury tests (levels of serum bile acids and indocyanine green [ICG] clearance rates) may be helpful in assessing liver status. Renal function tests (creatinine, BUN, electrolytes, and urinalysis) should be performed, and urine output and fluid balance should be

☐ **Liver and kidney function tests, chest X ray, and electrocardiogram are advised for persons exposed to CCl_4.**

monitored carefully. In persons with high exposures, clotting studies (i.e., PT and PTT), chest X ray, and electrocardiogram are warranted for baseline and monitoring purposes. If liver or renal injury is severe, patients should be evaluated for spontaneous bleeding with serial hematocrits and tests for stool occult blood.

Challenge

(4) Exposure to CCl_4 is confirmed. What are your immediate concerns regarding the prognosis of the acutely ill patient in the case study?

(5) What initial action should be taken in the emergency department for patients exposed to any volatile solvent (CCl_4 included)? What laboratory work-up is advised?

Treatment and Management

Liquid CCl_4 is absorbed through the skin; therefore, clothing should be removed from exposed persons and the skin cleansed with copious amounts of water and soap (or mild detergent). Because CCl_4 is somewhat irritating to mucous membranes, exposed eyes should be irrigated with water for at least 15 minutes. Gastric lavage and administration of activated charcoal are appropriate measures for patients who have ingested CCl_4. Do not induce emesis because pulmonary aspiration is a risk.

Case reports from Europe, where antioxidants such as methionine, cysteine, and N-acetylcysteine (NAC or MucoMyst®[*]) are used, suggest that when these free-radical scavengers are given intravenously within 12 to 15 hours after high-level, acute CCl_4 exposure, they may prevent or decrease hepatic and renal damage. Recommended intravenous use of NAC, which is currently investigational in the United States, is based on its success in the treatment of acetominophen overdose. The oral form of NAC, which is commercially available in the United States, also may prove useful. The clinician should consult with an experienced medical toxicologist or a regional poison control center.

Because of the suspected free-radical nature of a toxic intermediate in CCl_4 metabolism, the use of hyperbaric oxygen is contraindicated. Hemodialysis has been used to treat renal failure, but it has not proved successful in reversing CCl_4 pathology. Epinephrine should be used cautiously since it may induce or aggravate cardiac dysrhythmias.

Patients should be observed for onset of hepatic and renal effects up to 2 weeks after exposure. To a large extent, survival depends upon the patient's nutritional status and underlying condition of the hepatorenal system. Future hepatocellular carcinoma in persons with residual liver damage is a possibility. Exposed patients should be instructed to avoid stimulants and other hepatotoxicants including ethanol. Administration of the hepatitis B vaccine should be considered.

☐ **N-acetylcysteine may reduce complications in patients with severe CCl_4 exposure.**

☐ **Other than removal from the source of exposure and avoidance of other hepatotoxicants, no treatment for effects of chronic CCl_4 exposure exists.**

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[*] Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

Challenge

(6) What treatment would you recommend for the patient in the case study?

(7) What follow-up would you recommend for this patient? For his potentially exposed coworkers?

Standards and Regulations

NIOSH considers CCl_4 a probable human carcinogen and ACGIH considers CCl_4 a suspected human carcinogen. ACGIH also gives CCl_4 a "skin" designation, which indicates potential for dermal absorption. CCl_4 has an odor threshold of 10 parts per million (ppm), which does not provide adequate warning of harmful exposure. The regulations and guidelines pertaining to CCl_4 are summarized in Table 1.

Workplace

Air

The workroom standard for CCl_4, mandated by the Occupational Safety and Health Administration (OSHA), is a time-weighted average (TWA) of 2 ppm. NIOSH recommends a 60-minute ceiling limit of 2 ppm. The air level considered by NIOSH to be immediately dangerous to life and health (IDLH) is 300 ppm.

Environment

Air

Currently, there are no federal regulations for CCl_4 emissions into air; however, several state agencies have established maximum levels. CCl_4 is on the list of 190 hazardous air pollutants listed in the Clean Air Act, which was signed into law November 15, 1990. EPA is scheduled to issue CCl_4 emission standards by November 1992.

Table 1. Standards and regulations for carbon tetrachloride

Agency[*]	Focus	Level	Comments
ACGIH	Air-workplace	5 ppm (30 mg/m^3)	Advisory; TLV-TWA[†] (Skin)
NIOSH	Air-workplace	2 ppm (12.6 mg/m^3)	Advisory; Ceiling (60 minutes)
OSHA	Air-workplace	2 ppm (12.6 mg/m^3)	Regulation; PEL[‡] as TWA
EPA	Drinking water	5 ppb (0.005 mg/L)	MCL[¶]
		0	MCLG[**]

[*] ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency, NIOSH = National Institute for Occupational Safety and Health, OSHA = Occupational Safety and Health Administration

[†] TLV-TWA (Threshold Limit Value-Time Weighted Average) = time-weighted average concentration for a normal workday and a 40-hour workweek to which nearly all workers may be repeatedly exposed.

[‡] PEL (Permissible Exposure Limit) = highest level of CCl_4 in air to which a worker may be exposed, averaged over an 8-hour workday

[¶] MCL (Maximum Contaminant Level) = enforceable level for drinking water

[**] MCLG (Maximum Contaminant Level Goal)

Water

The EPA maximum contaminant level for CCl_4 in drinking water is 5 parts per billion (ppb). States have established maximum levels as low as 0.5 ppb (proposed for California).

Other

Federal regulations have banned the use of all pesticide products containing CCl_4; an exception is the use of CCl_4 on encased museum specimens.

Challenge

Additional information for the case study: You are requested to consult with the hazardous waste management company regarding the effect of CCl_4 exposure on employee health.

(8) What will you stress with management concerning this incident?

ATSDR

Suggested Reading List

General

Dossing M, Skinhoj P. Occupational liver injury. Present state of knowledge and future perspective. Int Arch Occup Environ Health 1985;56:1-21.

Guzelian PS. Hepatic injury due to environmental agents. Clin Lab Med 1984;4(3):483-8.

Hardin BL. Carbon tetrachloride poisoning — a review. Ind Med Surg 1954;23:93-105.

Louria DB, Bogden JD. The dangers from limited exposure to carbon tetrachloride. Crit Rev Toxicol 1980:7(2);177-88.

Zimmerman HJ. Effects of alcohol on other hepatotoxins. Alcohol Clin Exp Res 1986;10(1):3-15.

Treatment and Management

Meredith TJ, Ruprah M, Liddle A, Flanagan RJ. Diagnosis and treatment of acute poisoning with volatile substances. Hum Toxicol 1989;8(4):277-86.

Pond SM. Effects on the liver of chemicals encountered in the workplace. West J Med 1982;137(6):506-14.

Ruprah M, Mant TGK, Flanagan RJ. Acute carbon tetrachloride poisoning in 19 patients: implications for diagnosis and treatment. Lancet 1985;8436:1027-9.

Government Documents

Agency for Toxic Substances and Disease Registry. Toxicological profile for carbon tetrachloride. Atlanta: US Department of Health and Human Services, Public Health Service, 1989.

Environmental Protection Agency. Health effects assessment for carbon tetrachloride. Cincinnati: US Environmental Protection Agency, Office of Environmental Criteria and Assessment, 1989. Report no. EPA/600/8-89/088; NTIS report no. PB90-142407.

Sources of Information

More information on the adverse effects of carbon tetrachloride and treating and managing cases of exposure to carbon tetrachloride can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Carbon Tetrachloride Toxicity* is one of a series. For other publications in this series, please use the order form on the back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of the Director, at (404) 639-6204.

Answers to Pretest and Challenge Questions

Pretest

Pretest questions begin on page 1.

(a) Acute hepatic necrosis and renal impairment can occur up to 2 weeks after a CCl_4 exposure. Other secondary health effects reported include coagulation disorders, cardiac dysrhythmias, and pulmonary edema; these effects are not likely to resolve without improvement in the intercurrent kidney and liver disorders. Because of the patient's multiple exposures to hepatotoxic agents (i.e., recent heavy consumption of ethanol and potential occupational exposure), acute treatment should begin as soon as possible as a preventive measure.

(NOTE: It is unclear whether the isopropyl alcohol spilled on the patient's clothing will affect the patient's medical condition. Reports of isopropyl alcohol's ability to potentiate the harmful effects of CCl_4 are based on inhalation studies in experimental animals. Significant inhalation of isopropyl alcohol in this case is unlikely since the solvent does not volatilize readily. Isopropyl alcohol also is not absorbed readily by intact skin.)

Most cases of fatal CCl_4-induced hepatotoxicity involve persons with a history of heavy ethanol abuse. Although our patient consumed ethanol the night before the incident, he says he rarely imbibes, and most likely he has a healthy liver. Nevertheless, exposure to ethanol within 12 hours before CCl_4 exposure will potentiate CCl_4's toxicity. If the patient survives the first 2 weeks, the prognosis is good for complete recovery or for only mildly compromised liver and kidney function.

(b) Since samples were taken for analysis by the hazardous waste company, you should urge the company to complete this analysis as soon as possible. The history of the source plant as a chlorofluorocarbon manufacturer is suggestive of CCl_4 use. When the company identifies the material, you may request a Material Safety Data Sheet (MSDS). MSDSs often do not adequately meet the clinician's needs, however. More extensive documents, such as those in the *Suggested Reading List*, page 14, or the NIOSH *Current Intelligence Bulletin* for CCl_4 may be more helpful.

(c) Based on reports of treatment of patients with acetaminophen overdose, NAC given within approximately 12 hours after exposure may decrease the severity of both liver and kidney damage. Hemodialysis has been used in treating patients acutely exposed to CCl_4, but its success in reversing the pathology of CCl_4 has not been proven. Maintenance of normal hydration and a high protein diet (the latter only if tolerated) is suggested. Consultation with a gastroenterologist is indicated.

Challenge

Challenge questions begin on page 5.

(1) The older man's history of alcoholism and hepatitis B could put him at increased risk of CCl_4's adverse effects. Underlying liver damage would increase risk of acute effects and subsequent hepatocellular carcinoma. Although he was working in an appropriate protective suit and full-face respirator, it is unclear whether he has been exposed. His beard may have prevented proper fit of the respirator face piece. However, his symptoms could be due to working in a hot, enclosed space, or they may be psychophysiologic.

(2) It is not clear that this woman has been exposed to CCl_4. Her symptoms may be morning sickness associated with her pregnancy. However, it is important that she discuss this possible exposure with her obstetrician.

Although CCl_4 is lipophilic and may readily pass through the placenta to the fetus after maternal exposure, CCl_4 does not appear to be teratogenic in either animals or humans in the *early* stages of pregnancy. The human fetus typically develops the enzyme system necessary for the (toxic) metabolism of CCl_4 in the later months of pregnancy. Although it would be important to know if the mother is exposed to other exogenous MFO-inducing agents, it is doubtful that the 6-week-old fetus has been significantly affected. Nevertheless, it would be prudent to inform the parents and medical-care provider of the possible consequence of in utero exposure.

(3) Because the young man removed his respirator and presumably breathed the solvent for a prolonged time, he is at high risk. The odor was characterized as sweet smelling, which indicates that the air level was above 10 ppm (the CCl_4 odor threshold). His prior ethanol intake and possibly his concurrent exposure to isopropyl alcohol increase his risk. Alcohols can induce production of MFO enzymes, thereby potentiating the formation of CCl_4 toxic intermediates and metabolites.

(4) See answer to Pretest question (a).

(5) Initial actions include removing all contaminated clothing (since dermal absorption of some solvents is high) and cleansing the skin with mild soap and water. Care should be taken to prevent exposure of ED personnel to fumes from contaminated clothing; if possible, the patient should be decontaminated before entering the ED.

The following laboratory work-up is recommended for patients exposed to volatile solvents: baseline hepatic and renal function tests (i.e., SGOT [AST], SGPT [ALT], bilirubin, alkaline phosphatase, BUN, creatinine, electrolytes, and urinalysis), as well as PT, PTT, and CBC. Some solvents may cause dysrhythmias and pulmonary edema (probably secondary to renal toxicity); thus, a baseline electrocardiogram and chest X ray should be obtained. These tests should be repeated periodically to monitor the patient's condition.

You may wish to send blood and urine for a toxic substance screen concentrating on hepatotoxic agents such as acetaminophen and ethanol. If a laboratory is available that performs head space analysis by gas chromatography, a sealed, refrigerated blood sample can be analyzed for volatile solvents. The likelihood of confirming a patient's solvent exposure depends on the dose of solvent received, the time of sampling in relation to the time of exposure, and precautions taken during the collection and storage of the sample. Generally, analysis is most effective if performed within 24 hours after the exposure.

Appropriate public or occupational health reports should be filed. Some states may require that a doctor's first report of illness be filed with the state health department. These reports are often overlooked by ED physicians.

Challenge *(continued)*

(6) See answer to Pretest question (c).

(7) Immediate follow-up for the acutely ill patient consists of monitoring liver and kidney functions for up to 2 weeks. The patient's cardiac and pulmonary systems and clotting ability should also be evaluated periodically since abnormalities can occur secondary to hepatic and renal damage. If the patient shows no improvement, liver biopsy may be considered since liver enzyme levels are not always reliable predictors of liver damage. Liver biopsy is contraindicated in patients with coagulation disorders.

Persons exposed to CCl_4 who have survived without permanent physiologic damage have experienced nausea, dizziness, vision changes, abdominal pain, or delirium up to 24 hours after exposure. The patient's two coworkers, however, may suffer effects because of their unique circumstances. See answers to Challenge questions 1 and 2.

All three persons (the patient and his two coworkers) should be counseled to avoid other hepatotoxic agents such as ethanol, drugs, solvents, and chlorinated compounds. The 40-year-old worker (with possible liver injury as a result of alcoholism and hepatitis B), who was discharged the morning after the incident, and the acutely ill 25-year-old patient may be at increased risk for hepatocellular carcinoma; they should be monitored periodically. It may be advisable for the 25-year-old patient to get the hepatitis B vaccine as a preventive measure. The 30-year-old woman, who used full protective gear and whose symptoms disappeared quickly, is probably at minimal risk. See Challenge question and answer 2.

(8) It is important that the company establish a protocol for periodic health examinations of all employees. A complete exposure history for each employee should be maintained and made available to the physician. Under the OSHA Hazard Communication regulation (right-to-know provisions), MSDSs for hazardous chemicals in the workplace must be made available to the workers, their physician, and designated worker representative. All employees using a respirator should be fit-tested and all should be properly trained before entering a hazardous environment. Proper supervision is necessary at all times. Employees who are ill should not be allowed to remain at work, nor should employees be permitted to work without the requisite protective gear.

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Case Studies in Environmental Medicine

25

Chlordane Toxicity

Environmental ALERT . . .

- ☑ ***For over 35 years, chlordane was used as an agricultural insecticide and for termite control in and around homes.***
- ☑ ***EPA estimates that 19.5 million structures have been treated with chlordane; as many as 52 million occupants may be exposed.***
- ☑ ***Chlordane can persist in the environment for more than 30 years. Its residues are lipophilic and can remain in body fat stores for months.***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. See page 23 for more information about continuing medical education credits and continuing education units.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

A young couple with neurologic symptoms and loss of appetite

You are consulted by a couple in their mid-20s who moved to your southern rural community about 2 years ago and purchased an old farm. They have not felt well since their first winter in the home, when they began to experience general malaise and loss of appetite. They both have had transient nasal congestion and severe headaches that lasted 2 to 3 hours, sometimes accompanied by lightheadedness. These symptoms are especially noticeable after they work in their basement workshop. Once or twice, the wife was nauseated when she returned from the basement after several hours in the workshop.

In a recent conversation with their neighbor, your patients learned that the previous occupants, a young couple, had left the farm convinced that the wife's two miscarriages were due to termite fumigation of the house carried out 3 years before your patients moved in. They ask you if the association is possible, and whether this pesticide may also be the reason that they have not been able to conceive; they have not used birth control for about 1 ½ years.

On further questioning, you learn that the couple had been well before their move; they exercise regularly and are quite health-conscious. Neither has ever smoked tobacco, and they rarely drink alcohol. It was their desire to start a family and to seek a less stressful life that prompted them to leave their jobs in the city and to attempt organic farming. Further history reveals that the woman's last menstrual period was 5 weeks ago, but her menses have always been irregular. She has had no previous pregnancies.

Physical examinations are generally unrevealing. Complete blood counts, urinalyses, and chemistry profiles are all within normal limits, except for slight elevations of LDH and alkaline phosphatase in the man.

Pretest

(a) What problem lists would you consider for these patients?

(b) What further investigations would you consider doing at this time? Where could you obtain assistance in investigating these complaints?

(c) What is the likelihood that the miscarriages of the former occupant or the inability of these patients to conceive is related to the termite fumigation? Explain.

Answers to the Pretest questions are on page 17.

Exposure Pathways

☐ **Chlordane was used for more than 35 years as an termiticide and agricultural insecticide.**

Chlordane was the most commonly used member of the cyclodiene family of chlorinated insecticides that includes aldrin, dieldrin, and heptachlor. Depending on the degree of purity, chlordane may vary from a brown liquid to a white, crystalline solid. It has been described as odorless or having a chlorine-like or solvent-like odor. Technical or commercial-grade chlordane is a mixture of two chlordane isomers and more than 100 related reaction products. Chlordane manufactured before 1951 had a higher percentage of impurities than that produced later, which may have been responsible for some of the adverse health effects (especially irritant effects) associated with its earlier use. Trade names of chlordane-containing products include Chlor-Kil*, Dowchlor, Gold Crest C-100, Octa-Klor, Topiclor 20, and Velsicol 1068.

☐ **Indoor air contaminated by misapplication of chlordane is the greatest source of exposure risk for the general population.**

From about 1950 until it was banned, chlordane was used widely as a spray to protect structures against termites and to control insects on lawns, turf, ornamental plants, agricultural crops, and in drainage ditches. Subterranean injection of chlordane was also done to control termites. The amount of chlordane applied in the United States in the past 40 years is conservatively estimated at 200 million pounds; each year approximately 1.2 million homes were treated for termites.

☐ **Food grown on chlordane-contaminated land and fish from waters contaminated by agricultural runoff are potential sources of chlordane exposure.**

Concern about the risk of cancer and slow environmental degradation led the U.S. Environmental Protection Agency (EPA) to prohibit the use of chlordane on food crops in March 1978. Because no effective alternative chemicals were available at the time, chlordane's use for termite control continued until April 1988. Since then, both the sale and use of chlordane in the United States have ceased, and several foreign countries have banned it as well. Nevertheless, an estimated 40 to 75 million pounds of chlordane may still exist unaltered in the environment. Chlordane may be found in food, air, water, and soil, and most people have some form of it in their adipose tissue.

The major source of chlordane exposure today for the general U.S. population is indoor air, a result of the continuing volatilization from prior application in and around homes. Chlordane is usually undetectable in homes properly treated. However, homes treated improperly often have airborne levels of chlordane above the National Academy of Sciences (NAS) safety guideline of 5 micrograms per cubic meter ($5\ \mu g/m^3$) of air. Improper treatment includes pouring the chemical at the foundation line, carelessly injecting liquid chlordane directly into living spaces or air ducts, or spraying excessively in crawl spaces. If overspraying was done, emission of chlordane from joists and flooring can persist for 15 years after treatment. In addition to inhaling volatilized chlordane, persons can receive dermal exposure from contact with contaminated soil near treated houses or from previous

☐ **Except in unusual circumstances, chlordane is unlikely to reach and contaminate underground water sources.**

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* Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

lawn, garden, or agricultural application. In soil, chlordane resists chemical and microbial decomposition, remaining biologically active for 30 years or more.

Outdoor air contains only minute amounts of chlordane, primarily the result of volatilization from soil and water, as well as from wind erosion. Chlordane is readily degraded by photolysis and hydroxyl radical reactions, resulting in a half-life in outdoor air of about 1.3 days. In the environment, rain fallout and dry deposition are not significant transport mechanisms for chlordane.

Most chlordane water contamination occurs in surface water, the result of industrial releases, urban or rural runoff, or spraying near or over exposed bodies of water. In lakes or streams, chlordane adsorbs almost completely to sediment in about 6 days. Because it is lipophilic and is only slowly metabolized and cleared from the body of many species, it bioaccumulates in aquatic life and has the potential to concentrate in the food chain. Groundwater contamination is not likely to occur because chlordane adsorbs strongly to soils high in clay or organic material. Around waste sites, however, organic solvents can facilitate leaching, thereby allowing chlordane to reach underground aquifers.

Contaminated food is another source of chlordane exposure. Eating fish from chlordane-contaminated waters may add to a person's total body burden. Contaminated fish and other foods are assumed to account for 90% of the body burdens in the populations of Nordic countries where chlordane use was minimal. Certain crops, especially corn, can absorb chlordane from previously treated soil. The daily U.S. intake of chlordane from all sources is estimated to be 0.1 micrograms per kilogram of body weight per day (0.1 µg/kg/day). The World Health Organization (WHO) recommends an upper limit acceptable daily intake (ADI) of 1 µg/kg/day.

Challenge

Additional information for the case study: The couple found a closed, half-empty bucket of a white powder in their basement. The label, which has been partially destroyed, has the words Topiclor 20, but the ingredients cannot be discerned. However, the directions that are legible include the words termiticide *and* insecticide.

(1) If this bucket contains chlordane that was previously used on the farm, what are the most likely exposure sources for the patients in the case study?

Who's at Risk

☐ **EPA estimates that 52 million persons are potentially exposed to chlordane in their homes.**

Persons with the greatest exposure to chlordane are most likely to be those employed in occupations in which handling the pesticide is common, including manufacture, distribution, and application. Because chlordane is now banned commercially in the United States, the only current occupational exposures would be from chlordane manufactured for export and from chlordane disposal. Chlordane has been found at 166 of 1300 hazardous waste sites on the EPA National Priorities List.

When chlordane was available commercially, most cases of systemic chlordane toxicity occurred after acute dermal exposure or accidental or suicidal ingestion. Today, most people at increased risk of chlordane exposure (primarily via inhalation) are occupants of houses previously treated for termite control. Chlordane was used throughout much of the United States, but most treated structures are located in the South and far West, where termite infestations are a significant problem.

In 1987, EPA estimated that as many as 52 million persons may be exposed to chlordane in their homes. Most homes have been treated properly, and the occupants are unlikely to experience adverse effects. However, it is not known what percentage of homes have been treated improperly; even a small percentage could affect a large number of persons.

☐ **Infants may be at increased risk if the mother has had significant chlordane exposure.**

Children may have increased exposure risk. A chlordane metabolite, heptachlor epoxide, has been detected in maternal and fetal blood and in amniotic fluid, indicating potential exposure in utero. Chlordane accumulates in breast milk, which may increase the risk for nursing infants of significantly exposed mothers. In several surveys of nursing mothers who had no known exposures, chlordane or its metabolites were found in more than 50% of breast milk samples, but the levels found appeared to have no short-term effects on the infants. Children's diet may contribute to their total body burden of this fat-soluble pesticide because they generally drink more milk and eat more foods that are high in fat content than do adults.

Chlordane is metabolized in the liver, where it leads to enzyme induction of the cytochrome P-450 system. Enzyme induction can accelerate the metabolism of many drugs and hormones, requiring dosage adjustments in chlordane-exposed patients taking these medications.

Challenge

Additional information for the case study: Two weeks after the couple's initial visit, the woman's pregnancy test is positive.

(2) What advice can you give these prospective parents about potential prenatal and postnatal exposure of the infant?

Biologic Fate

Chlordane is absorbed well by all exposure routes. It has caused fatalities after ingestion or skin contact. An acute oral dose as low as 25 milligrams/kilogram (mg/kg) has caused death in humans. This is about tenfold lower than the oral LD_{50} dose reported for experimental animals. (The LD_{50} is the dose that is fatal to 50% of an experimental animal population; the lower the LD_{50}, the more toxic the agent is.) The lethal dermal dose for humans is not known, but dermal LD_{50} values in animals are low. Once absorbed, chlordane is distributed rapidly throughout the body. Concentrations of chlordane and its metabolites are highest in adipose tissue, spleen, brain, kidney, liver, and breast milk.

☐ **Chlordane is absorbed systemically after ingestion, inhalation, and skin contact.**

The hepatic metabolism of chlordane, which occurs slowly, has not been studied well in humans. Animal studies show that four metabolic pathways probably exist. The primary metabolites—oxychlordane, nonachlor, heptachlor, and heptachlor epoxide—are more toxic than the parent compound.

☐ **Chlordane and its metabolites are preferentially stored in adipose tissue.**

Chlordane and its metabolites are preferentially stored in adipose tissues, and concentrations increase as exposure duration increases. Oxychlordane is the major metabolite in most species and can account for up to 90% of the chlordane residues in adipose tissue. In acute or subacute poisoning, the fat-to-serum ratio of chlordane residues can be as much as 100:1.

☐ **Excretion of a chlordane dose may take weeks to months.**

Chlordane metabolites are excreted mainly in the feces and, to a lesser degree, in the urine. Excretion is slow, taking weeks to months. Breast milk is a major route of excretion in lactating females. The metabolite oxychlordane has been reported in milk samples of women with no known chlordane exposure at concentrations ranging from 2 to 5 μg oxychlordane per liter of whole milk (2 to 5 parts per billion [ppb]). Concentrations of total chlordane residues in breast milk of mothers with chronic inhalation exposure were up to 188 ppb.

Physiologic Effects

☐ **Chlordane affects primarily the nervous system and the liver.**

Acute or chronic chlordane exposure may affect the neurologic and hepatic systems. Adverse respiratory and gastrointestinal effects from acute chlordane inhalation or skin contact are generally secondary to central nervous system (CNS) effects. Chlordane was often used as a spray, in which case it was dissolved in a petroleum distillate solvent. The solvent itself could produce adverse health effects. Because of experimental animal data, EPA considers chlordane a probable human carcinogen.

Neurologic Effects

☐ **Chlordane disrupts nerve transmissions and causes neuronal irritability.**

In experimental animal studies, chlordane significantly inhibited brain adenosine triphosphatase (ATPase), which may be involved in the mechanism of chlordane-induced neurotoxicity. Acute chlordane exposure in humans (usually an overdose or suicide attempt) has produced CNS excitation, generalized seizures that were difficult to control, and respiratory depression. Other CNS effects reported in acute and chronic poisonings have included confusion, irritability, hyperexcitability, hyperreflexia, loss of coordination, excessive salivation, muscle twitching and tremors, and coma.

Hepatic Effects

☐ **In experimental animals, chlordane is quite hepatotoxic.**

Liver damage (including hepatocellular carcinomas and adenomas) has been noted in chronic feeding studies in experimental animals, yet only mild hepatotoxic effects (e.g., jaundice; increased serum levels of triglycerides, creatine kinase, and lactic dehydrogenase; and hepatomegaly) have been reported in chronically exposed humans. A causal relationship between chlordane exposure and hepatotoxicity in humans remains uncertain, and more research is required to evaluate hepatic effects in chlordane-exposed persons.

Gastrointestinal Effects

Anorexia, nausea, and vomiting can occur in acute or subacute chlordane poisonings by any exposure route, and anorexia and nausea may persist for months. In cases of inhalation and dermal exposure, these effects are most likely secondary to CNS effects. After deliberate ingestion in one case, chemical burns in the mouth, hemorrhagic gastritis, and hematochezia (passage of bloody stools) were reported; the material ingested may have been an older chlordane preparation that contained highly irritating hexachlorocyclopentadiene. Chlordane produced after 1951 does not contain this impurity and is nonirritating. Vomiting after ingestion of some chlordane preparations can result in pulmonary aspiration of the solvent vehicle, which may cause lipoid pneumonitis.

☐ **Gastrointestinal effects may result after chlordane exposure by any route.**

Carcinogenicity

Results of various epidemiologic studies regarding chlordane's carcinogenicity in humans are conflicting and inconclusive. Some studies have suggested a relationship between chlordane exposure and development of brain, blood, lung, or bladder cancers. However, studies of chlordane-manufacturing workers (theoretically the population that would receive the greatest exposure) do not confirm the relationship between chlordane exposure and cancer mortality.

☐ **Because of experimental animal data, EPA considers chlordane a probable human carcinogen.**

Because of the increased incidence of hepatocellular carcinomas in some experimental animals exposed to chlordane in their diet, EPA has placed chlordane in its Class B2 (probable human carcinogen) category. The International Agency for Research on Cancer (IARC) considers the evidence for carcinogenesis induced by chlordane limited in animals and inadequate in humans.

Other Effects

Various blood dyscrasias have been associated with chronic environmental exposure to chlordane, but not with occupational exposure. The blood dyscrasias noted have included aplastic anemia, refractory megaloblastic anemia, thrombocytopenic purpura, acute lymphoblastic leukemia, and acute myelocytic leukemia. The low incidence of most blood dyscrasias limits the feasibility of an epidemiologic study, and the association between these diseases and chlordane has been made on the basis of case reports. A clear causal relationship has not been shown.

☐ **Various blood dyscrasias have been associated with environmental chlordane exposures, but the evidence is anecdotal and inconclusive.**

No studies regarding reproductive or developmental effects of chlordane in humans have been reported. When chlordane was administered by gavage to experimental animals, effects in offspring ranged from decreased fertility to hematopoietic and neurologic disorders.

☐ **No data on reproductive and developmental effects of chlordane in humans are available.**

Challenge

(3) Are the complaints of the patients in the case study consistent with chlordane exposure?

(4) What can you tell them about potential cancer risks?

Clinical Evaluation

History and Physical Examination

☐ **Patients who are chronically exposed to chlordane may develop a variety of nonspecific complaints.**

☐ **Environmentally exposed patients often undergo considerable diagnostic testing before a connection is made with a possible toxic exposure.**

Because chlordane has been used extensively and persists in the environment, chronic chlordane poisoning is a concern. Acute poisoning is less likely because chlordane has not been available commercially since its ban in 1988, although private stocks may still be accessible.

Diagnosis of chlordane toxicity is based on history of exposure, examination, and confirmatory laboratory or environmental testing. Persons chronically exposed to chlordane, with signs and symptoms of poisoning, have usually undergone a significant amount of diagnostic testing before being questioned about a possible toxic exposure. At a minimum, the medical history should include the following:

- occupational history
- residence: age, pest control use, location in relation to industrial facilities or hazardous waste sites
- hobbies, including gardening
- medications

(For more information, see *Case Studies in Environmental Medicine: Taking an Exposure History.*)

If chlordane ingestion is suspected, the physical examination should include a careful neurologic examination looking for hyperreflexia, tremors, and myoclonus. The abdomen should be palpated for hepatomegaly.

☐ **Chlordane and metabolite levels can be measured in blood and adipose tissue, but the results do not correlate with degree of toxicity.**

An incident of chlordane toxicity may be a sentinel event. Other persons, such as household occupants or coworkers, may be similarly exposed. Nervous system complaints, pulmonary complaints, fatigue, and appetite loss—symptoms compatible with exposure to chlordane or a similar pesticide—in more than one family member should increase the index of suspicion for toxic exposure.

Signs and Symptoms

Acute Exposure

Acute chlordane poisoning is characterized by the rapid development of violent, generalized seizures between ½ to 3 hours after exposure. Nausea and vomiting can occur before the onset of seizures. Respiratory depression and cyanosis may develop secondary to convulsions. Mental confusion, apprehension, diplopia, blurred vision, muscle twitching and tremors, myoclonus, incoordination, ataxia, hyperexcitability, and coma are also signs of chlordane toxicity. Mania and convulsions culminating in death have been reported with acute ingestion exposure.

☐ **Generalized seizures are common in persons with acute chlordane poisoning.**

Chronic Exposure

Persons chronically exposed to chlordane in termiticide-treated homes have complained of adverse effects such as headaches, nausea, lightheadedness, syncopal episodes, muscle twitching and tremors, fatigue, weakness, and visual disturbances. In one study of persons living in contaminated homes, a dose-response relationship was found for sinusitis, bronchitis, and migraine-type headaches. Hepatomegaly may also develop in chronically exposed persons. Although evidence linking blood dyscrasias with chlorinated compounds is inconclusive, persons with aplastic anemia or leukemia should have their environmental and occupational histories explored thoroughly for chronic exposure to chlordane (or other organochlorine compounds).

☐ **Patients with chronic chlordane exposure usually have neurologic complaints.**

Laboratory Tests

Because mild hepatotoxicity has occurred in some patients with chlordane poisoning, liver-function tests would be appropriate. A complete blood count and urinalysis should also be obtained. If neurologic complaints are present, nerve conduction velocity testing and electromyograms may be useful. In patients who have seizures or severe headaches, intracranial mass lesions and idiopathic epilepsy should be ruled out.

When possible, chlordane levels in various areas in the home and surrounding soil should be measured before performing chlordane testing in biologic samples. If high levels are found in the person's environment, blood or adipose tissue levels of chlordane and its metabolites may confirm exposure and assist in diagnosis. However, because there is no known relationship between chlordane levels in the body and adverse health effects, measuring chlordane levels in biologic samples is generally not helpful in managing symptomatic chlordane poisoning.

Testing for chlordane in biologic samples is usually reserved for research. In the United States, a national study conducted from 1972 to 1983 on adipose tissue samples obtained during autopsies found average oxychlordane levels around 100 ppb (range, 30 to 500 ppb). Similarly, concentrations of chlordane in human adipose tissue specimens from around the world have generally been in the parts per billion range. Blood levels of total chlordane metabolites in pest control operators have ranged from 0.3 ppb after only 1 day of spraying to 5.6 ppb after 27 days of spraying.

Challenge

(5) Assuming chronic chlordane exposure for the couple in the case study, what further physical examination is suggested?

(6) What additional diagnostic testing might be considered?

Treatment and Management

Acute Exposure

There is no antidote for chlordane poisoning. If CNS, respiratory depression, or continuous seizures occur, airway patency and adequacy of oxygenation should be assured. Most seizures can be controlled by standard measures, using diazepam, phenobarbital, or phenytoin. Induced diuresis, hemodialysis, and hemoperfusion have not been shown to be effective for acute chlordane poisoning.

☐ **Seizure control and maintenance of adequate respiration and oxygenation are primary concerns in the treatment of acute chlordane poisoning.**

Emesis should not be induced in patients who have ingested chlordane because of the danger of pulmonary aspiration of gastric contents if seizures or CNS depression occur. Gastric aspiration and lavage may be of benefit if done within the first hour after ingestion. Because chlordane has some enterohepatic recirculation, multiple doses of activated charcoal may be considered in serious poisoning.

☐ **There is no antidote for chlordane poisoning; treatment consists of supportive measures.**

If skin exposure has occurred, contaminated clothing should be removed and the skin and hair washed several times with mild soap and shampoo, rinsing each time with copious water. Exposed eyes should be irrigated with tepid water or normal saline for at least 15 minutes.

Chronic Exposure

Assessing the environment and preventing further exposure are the most important steps in managing cases of chronic exposure to chlordane. Local or state health and environmental officials, EPA, or the National Pesticide Telecommunications Network (24-hour hotline [800]858-7378) can help locate companies that measure chlordane levels in indoor air and soil surrounding a potentially contaminated dwelling. Decontamination or other mitigation methods should not be undertaken without first obtaining advice from public health or environmental professionals. (For further information on chlordane mitigation, see the attached Chlordane Environmental Fact Sheet.)

☐ **Preventing further exposure is an important step in managing chronic chlordane poisoning. However, abatement and remediation measures to decontaminate homes should not be undertaken without professional guidance.**

No treatment specific for chlordane poisoning exists. Binding agents, such as cholestyramine, have been suggested to increase fecal elimination. However, clinical experience with this treatment modality is limited, and its effectiveness in chlordane poisoning is unproven.

☐ **Administering cholestyramine may increase chlordane excretion, but clinical experience with this treatment is limited.**

Challenge

Additional information for the case study: The results of air testing in the couple's home reveal average chlordane levels of 72 $\mu g/m^3$ in the basement and 16 $\mu g/m^3$ in the living space. The testing was conducted under conditions that would maximize test results; that is, the house had been closed for 2 hours before testing began, and testing was done during a time when the heat was on and the humidity was low. Soil samples taken at 10 and 100 yards from the house and samples from the garden reveal significant chlordane contamination.

(7) What measures could the couple take to reduce their exposure to chlordane?

(8) Would administration of cholestyramine be useful in treating the couple?

Standards and Regulations

On March 6, 1978, registrations for all uses of chlordane on food crops were cancelled. Chlordane use on nonedible plants and its continued use for subterranean termite control were phased out over the following 5 years. In 1987, a negotiated agreement was reached with the primary U.S. chlordane manufacturer, banning the sale, distribution, and use of chlordane, effective April 14, 1988. The U.S. regulations and guidelines pertaining to chlordane in air, water, and food are summarized below. There are no guidelines for chlordane in soil.

Workplace

The workplace standard mandated by the Occupational Safety and Health Administration (OSHA) is a time-weighted average (TWA) of 0.5 milligrams per cubic meter of air (mg/m^3), which is also the recommendation of the American Conference of Governmental Industrial Hygienists (ACGIH) and the National Institute for Occupational Safety and Health (NIOSH).

Environment

Air

There are no federal regulations for chlordane in ambient air. In 1979, NAS established an interim exposure guideline for indoor airborne concentrations of chlordane, which recommended that the level not exceed 5 μg/m^3.

Water

To protect human health from the potential carcinogenic effects of chlordane through the ingestion of contaminated water and aquatic organisms, EPA regulates the level of chlordane in drinking water and has established guidelines to keep other water supplies safe. The enforceable maximum contaminant level (MCL) for public drinking water supplies is 2 μg/L (2 ppb). To protect freshwater aquatic life, EPA recommends that the water concentration in any body of water never exceed 2.4 μg/L (2.4 ppb). Chlordane is being considered for inclusion on the National Priority Drinking Water Regulation List. The nonenforceable maximum contaminant level goal (MCLG) for drinking water is zero. The WHO-recommended drinking water guideline is 0.3 μg/L (0.3 ppb).

Food

The Food and Drug Administration (FDA) has set action levels in food or feed to regulate residues of certain pesticides for which there are no tolerances. Action levels for chlordane include 0.1 ppm in many fruits, vegetables, and berries; and 0.3 ppm in fish or animal fat (rendered). The Food and Agricultural Organization/World Health Organization (FAO/WHO) has set an acceptable daily intake (ADI) for chlordane at 1 μg/kg.

Table 1. Standards and regulations for chlordane

Agency[*]	Focus	Level	Comments
ACGIH	Air-workplace	0.5 mg/m^3 (skin designation)	Advisory; TLV-TWA[†]
NIOSH	Air-workplace	0.5 mg/m^3 (skin designation)	Advisory; REL[§]as TWA
OSHA	Air-workplace	0.5 mg/m^3 (skin designation)	Regulation; PEL[¶]as TWA
NAS	Air-indoor	0.005 mg/m^3	Advisory
EPA	Drinking Water	2 ppb	Regulation MCL[**]
		0 ppb	Advisory; MCLG[††]
	Fresh water (aquatic)	2.4 ppb	Regulation
WHO	Drinking water	0.3 ppb	Advisory
FDA	Food Residual chlordane:		
	in food crops	0.1 ppm	Regulation
	in fish	0.3 ppm	Regulation
	in animal fat (rendered)	0.3 ppm	Regulation

[*] ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; NAS = National Academy of Sciences; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; WHO = World Health Organization

[†] TLV-TWA (threshold limit value-time-weighted average) = time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[§] REL (recommended exposure limit) = recommended level in air to which a worker may be exposed, averaged over an 8-hour workday.

[¶] PEL (permissible exposure limit) = legal concentration in air to which a worker may be exposed, averaged over an 8-hour workday.

[**] MCL (maximum contaminant level) = enforceable level for drinking water.

[††] MCLG (maximum contaminant level goal) = nonenforceable level for drinking water.

Suggested Reading List

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ANSWERS TO PRETEST AND CHALLENGE QUESTIONS

Pretest questions are on page 1. Challenge questions begin on page 3.

Pretest

(a) The problem lists for the man and woman include nasal congestion, fatigue, severe headaches, lightheadedness, and loss of appetite. In addition, the problem list for the woman includes nausea, amenorrhea, and possibly pregnancy.

(b) Further investigations might include additional laboratory testing and seeking more information about the couple's present and past home and work environments. You might contact a public health official or the National Pesticide Telecommunication Network ([800] 858-7378) to discuss the patients' symptoms and to determine if the termite fumigation could play a role. You could recommend that the couple increase ventilation in the house, especially the basement, and limit the time spent in the basement workshop. Encouraging the couple to keep a journal of their symptoms and activities could help to determine the effectiveness of these measures. If the symptoms persist, the journal could help to confirm a temporal relationship between symptom onset and activities. Advising the couple to have the indoor air tested is also a possibility.

(c) The association is unknown. The termiticides in use in 1987 (about the time of the termite fumigation) were organochlorine compounds, namely chlordane, dieldrin, aldrin, heptachlor, and endrin. Because the house is located in the South, it is probable the termiticide was chlordane. Although chronic exposure to chlordane has caused a variety of reproductive and developmental toxicities in experimental animals exposed by gavage, no data are available to assess these effects in humans.

Challenge

(1) Because of the southern location, the house could have been treated with chlordane for termite control, resulting in potential exposure through inhalation of contaminated indoor air. If chlordane was used as an insecticide on the crops grown on the farm, it is most likely still in the soil because chlordane persists for 20 years or more in soil. Eating crops grown in contaminated soil would be a potential exposure source for the couple because some crops (especially corn and soybeans) can absorb chlordane from treated soil. The couple might also be exposed dermally by handling contaminated soil or by kneeling while gardening in contaminated soil. Another potential exposure source is water contaminated by aerial spraying or by runoff from contaminated fields.

Unused pesticides should be disposed of. See Chlordane Environmental Fact Sheet, page 19, for organizations to contact for advice on proper disposal.

(2) Although chlordane has been found in umbilical cord blood and amniotic fluid, little is known about effects on the human fetus exposed to chlordane in utero. If the woman is chronically poisoned with chlordane, the pesticide will be excreted in the breast milk, thus exposing the nursing infant. Before the infant is breast-fed, a sample of the mother's milk could be analyzed for chlordane and its metabolites. Consultation with a medical toxicologist may be advisable.

(3) Yes, neurologic complaints and nasal congestion are effects reported by inhabitants of houses that were improperly treated with chlordane. However, such nonspecific symptoms as nausea, anorexia, lightheadedness, and headaches are obviously not unique to chlordane.

(4) The risk of developing cancer from chronic chlordane exposure is presently undefined, although EPA considers chlordane a potential human carcinogen on the basis of experimental animal data.

(5) Further physical examination might include careful palpation of the abdomen for signs of hepatomegaly and a careful neurologic examination. Hyperreflexia, muscle tremors, and myoclonus may be present in chronically exposed residents of houses treated improperly with chlordane.

(6) Diagnostic evaluation would include liver-function tests and neurologic testing. If the history and clinical indications warrant, a CT (computerized tomography) scan or MRI (magnetic resonance imaging) may be appropriate to rule out intracranial pathology as a cause of the headaches. Further hematologic testing might be needed if CBC results are abnormal.

(7) Abatement and decontamination measures should be undertaken only with advice from a remediation specialist or other environmental professionals. Steps that can be taken to reduce the chlordane level of indoor air are increasing the ventilation; applying barrier coatings to contaminated walls, floors, and joists; removing or encapsulating chlordane-impregnated topsoil; and modifying the building's structure (see page 20 in the attached Chlordane Environmental Fact Sheet). The couple should also discuss the soil contamination with an agricultural pesticide expert or consider having garden produce tested for chlordane and its residues before they continue to consume it.

(8) Cholestyramine has been shown to increase the fecal excretion of absorbed chlordane; however, clinical experience with this treatment modality is minimal, and its efficacy is unproven in treating chlordane-exposed patients. Therefore, it cannot be recommended in this case.

Cholestyramine has been given safely to pregnant women for other indications, but there have been no controlled trials of its safety. When cholestyramine is administered to a pregnant patient, supplementation with prenatal vitamins 2 to 3 hours after dosing is recommended because cholestyramine decreases the absorption of fat-soluble vitamins such as A, K, and D. Consultation with a medical toxicologist or regional poison control center is advisable before beginning therapy.

Sources of Information

More information on treating patients exposed to chlordane can be obtained from ATSDR, the National Pesticide Telecommunications Network (24-hour hotline, [800] 858-7378), your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Chlordane Toxicity* is one of a series. To obtain other publications in this series, please use the order form on the inside back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of the Director, at (404) 639-6204.

Chlordane Environmental Fact Sheet

How does chlordane get inside houses?

Vapors can enter houses after proper or improper application of chlordane and other termiticides.

> Proper application: Factors that may contribute to vapors entering the home include cracks in concrete floors and walls, floor drains, sumps, joints, cracks in hollow block walls, and air ducts (heating, cooling, and ventilation ducts).
>
> Improper application: Indoor contamination can arise from careless injection of liquid chlordane directly into the living space of a house, onto interior walls, or into air ducts located in or below the slab. Surface spraying the soil or the wood in a crawl space is illegal in most states. **In fact, any indoor surface spraying of chlordane is an improper application.**
>
> Plenum construction: In this type of construction, air is circulated without ductwork through the open area below the house. This allows chlordane vapors to be drawn out of the soil and into the air of the house. Many chlordane labels prohibited application to plenum structures.

Once chlordane vapors get inside a house, what happens?

Chlordane vapors tend to persist inside a house. Indoor air monitoring studies conducted in homes treated properly with termiticides indicate that approximately 90% of the homes treated with chlordane have detectable levels of chlordane in the air 1 year after treatment. These studies also show that houses built on slabs (on the surface of the ground) had lower levels than houses with a basement or a crawl space. Basement rooms had the highest levels. Chlordane has also been found in the soil of treated areas 30 years or more after treatment.

Does the existence of chlordane vapors inside a house necessarily affect the occupants' health?

Although human exposure to chlordane in the home may increase certain health risks, most people who are exposed are not likely to develop these health conditions. The individual risk of developing adverse symptoms is low. Health risks depend on the duration of exposure and the concentration of chemical involved.

In humans, exposure to high levels commonly associated with misuse of chlordane has produced symptoms of headaches, dizziness, muscle twitching, weakness, tingling sensations, and nausea. However, these symptoms may also indicate a wide variety of illnesses unrelated to chlordane exposure. EPA also has concerns about long-term damage to the liver and the central nervous system. In addition, experimental animals exposed to chlordane over a lifetime have developed tumors. The long-term effects in humans exposed at levels lower than those likely to occur from misuse are not known.

How does one know if a house was treated with chlordane?

If a house was treated for subterranean termites before 1981, it is likely that chlordane was used. Also, before 1983, chlordane may have been used in the interior to control other household insects such as ants. Although new termiticides have been approved for use since 1981, chlordane was the one most commonly used before that date. If possible, contact the builder or pest control company that treated the home to determine what chemical was used for treatment.

If chlordane was used, how can the indoor air quality be improved?

The following suggestions will minimize occupants' exposure to chlordane and other indoor air pollutants (e.g., radon).

- Increase the circulation of clean air into the house. When weather permits, periodically open windows and doors, and use fans to mix the air. In crawl spaces, clear or add vents and install a fan to constantly vent crawl-space air to the outside.

- Seal areas that directly come in contact with treated soil, using grout, caulk, or sealant. Fill cracks in basement and ground floors and walls, joints between floors and walls, and openings around pipes, drains, and sumps. Periodically check these areas for signs of new cracks or broken seals because houses settle over time.

- Install a system that supplies outside air to appliances like clothes dryers and furnaces or fireplaces that normally draw air from inside the house. These may actually create a negative pressure within the house and help draw chlordane vapors from the soil into the house through walls, floors, and basements.

- Check the condition of ducts in the crawl space or basement. Use duct tape to seal openings and joints.

If chlordane misapplication is suspected, what can be done?

If improper application of chlordane is suspected, the suggestions above should be followed to improve the indoor air quality. In addition, the air in the home should be tested. Indications of misapplication may include the following:

- the presence of odors inside the house
- an increase in such odors when the heating or cooling system is operating
- evidence of a potential chlordane spill, such as stains, in the house
- similar symptoms in several household occupants

How can a house be tested?

It is important to ensure that the results of air testing are reliable by having qualified laboratory personnel collect and analyze air samples. A laboratory proficient in both indoor air sampling and pesticide analysis should be used. This type of service is generally available only from commercial laboratories. Costs vary according to the amount of testing, but could range from about $50 to $500. To locate a laboratory in the area, you can call the National Pesticide Telecommunications Network (NPTN) at (800) 858-7378 or contact your state or local health department.

How does a person interpret the test results?

In 1982, the National Academy of Sciences published interim guidelines for airborne levels of a number of termiticides. The recommended safe level for chlordane is 5 $\mu g/m^3$. This guideline is not a critical cut-off point, however. The conditions under which the air sampling was performed will influence the test results. Levels will be higher if the house was closed prior to sampling and if the heat was on, but lower if the humidity is high. A qualified professional should be consulted before abatement or other remedial procedures are undertaken to reduce indoor levels.

What additional steps can be taken to reduce exposure?

If the above suggestions for improving indoor air quality have been followed, the air in the house has been tested, and the air sample results are high, structural modifications may be useful to further reduce the level of chlordane. For homes that were treated properly, modifications are probably not worth the high expense. Modifications must be designed on a case-by-case basis, but may include replacing or relocating air ducts, replacing furnaces or ventilation systems with air exchangers, using barrier coatings of polyvinylidene chloride (e.g., Saranex) or polyamide (e.g., Capran-C), or sealing crawl-space soil with a layer of concrete. Decontamination measures or other mitigation methods should not be undertaken without professional advice.

How can one dispose of unwanted chlordane?

Chlordane can be a serious hazard to the environment as well as to human health. It is illegal to dump chlordane into sinks, toilets, storm drains, or any body of water. Any unused pesticide or its container must be disposed of according to both the instructions on the label and state laws. For clarification of label directions or additional guidance, call NPTN or contact your state pesticide or environmental control agency or a hazardous waste representative at the nearest EPA regional office.

Are any alternatives to chlordane available?

As of July 1987, two alternative termiticides, chlorpyrifos (e.g., Dursban) and permethrin (i.e., Torpedo and Dragnet) were registered with EPA and are available commercially. Chlorpyrifos is an organophosphate pesticide (see *Case Studies in Environmental Medicine: Cholinesterase-Inhibiting Pesticide Toxicity*), and permethrin is a synthetic pyrethroid pesticide. EPA has concluded that these termiticides, when used according to label directions, do not pose unreasonable risks.

How can I get more information?

Call the NPTN 24-hour hotline at (800) 858-7378.

Chronic Reactive Airway Disease following Acute Chlorine Gas Exposure in an Asymptomatic Atopic Patient*

Brad B. Moore, M.D., and Michael Sherman, M.D., F.C.C.P.

While chlorine gas inhalation has previously been reported to cause temporary mucous membrane irritation, acute pneumonitis, pulmonary edema, and transient bronchospasm, there is controversy about the existence of long-term pulmonary sequelae. We report the case of a 25-year-old man in whom chronic, recurrent asthma developed after exposure to a chlorine gas leak in an enclosed space. His course since the exposure has been notable for frequent exacerbations necessitating chronic corticosteroid therapy and multiple hospitalizations. To our knowledge, the persistence of symptoms years after the exposure is unique in the literature. ***(Chest 1991; 100:855-56)***

Chlorine is widely used in water purification and in the manufacture of plastics, bleaches, and alkalis. Although its pungent odor is detected in concentrations as low as 0.5 ppm, it causes respiratory damage only at levels above 20 ppm. Discovery of the highly toxic effects of chlorine gas on the human respiratory tract resulted in its deployment as the first chemical weapon at Ypres, France, in 1915. Despite extensive study since that time, controversy still exists about long-term pulmonary sequelae after acute chlorine-induced lung injury. We report a unique case of severe, chronic asthma following acute exposure to chlorine gas.

CASE REPORT

A 25-year-old man came to the Hahnemann University Hospital Emergency Room with severe dyspnea. He had a history of mild childhood asthma, which had resolved at the age of 5 years. Four years prior to admission, the patient was exposed to a chlorine gas leak while working for a regional sewerage authority. The patient had worked for 2 h in a chlorine-filled enclosed environment without a protective respirator mask. Immediately following this exposure, the patient experienced a transient episode of hemoptysis followed by acute shortness of breath and wheezing. A regimen of aminophylline and inhaled beta-agonists was started in a local emergency room, which resulted in some improvement in his symptoms. His course over the next 4 years was notable for frequent hospitalizations for asthma and increasing use of oral and inhaled corticosteroids. He was admitted to Hahnemann University Hospital for management of an acute exacerbation of his illness and a diagnostic workup.

Physical examination revealed an afebrile, cushingoid patient in moderate respiratory distress. Auscultation of the chest revealed diffuse expiratory wheezes in all lung fields with prolonged expiration.

An arterial blood gas evaluation on room air revealed a pH of 7.45, a Pco_2 of 32.2, and a Po_2 of 73.6. The eosinophil count was 8 cu mm, the immunoglobulin G activity was markedly elevated at 431 U/ml (normal, <122 U/ml). A chest roentgenogram was normal except for minimal peribronchial thickening. An esophagram demonstrated minimal gastroesophageal reflux without aspiration. An *Aspergillus* skin test was negative. A flow volume loop and otorhinolaryngologic evaluation showed no evidence of upper airway obstruction. Pulmonary function testing revealed an FVC of 2.71 (52 percent of the predicted value [PV]), an FEV_1 of 1.42 (35 percent of PV), an FEV_1/FVC of 52 percent, an FRC of 5.09 (154 percent of PV), and a TLC of 7.43 (107 percent of PV)—values consistent with severe obstruction (normal values from Crapo et al[1]). Administration of aerosolized albuterol produced a 54 percent improvement in FEV_1 and a 26 percent improvement in FVC, which was reproduced in multiple studies. The single breath diffusion capacity for carbon monoxide was 31.95 (89 percent).

Intravenous methylprednisolone, intravenous aminophylline, and aerosolized terbutaline were given with significant improvement in the patient's symptoms and flow rates, although moderate obstruction remained. After several days, the patient was discharged on a regimen of high-dose oral corticosteroids with persistent airflow obstruction.

DISCUSSION

Although today most reported cases of chlorine exposure occur in industrial settings,[2,3] at water treatment facilities,[4] or as a result of transportation accidents,[5,6] several cases of toxic chlorine inhalation have occurred in more unusual circumstances. An increasingly common source of exposure to chlorine gas is fumes liberated from chlorine products used in residential pools and spas.[7,8] Cases of exposure resulting from chlorine gas released during mixing of a variety of household cleaning agents[9] have prompted the placement of consumer warnings on many such products. One episode of voluntary exposure has also been reported.[10]

The long-term pulmonary sequelae of chlorine gas inhalation are controversial. Studies of soldiers gassed during the First World War showed evidence of obstructive airway disease and permanent disability.[8,11] It is difficult to ascribe abnormalities found in these patients solely to chlorine inhalation for two reasons: chlorine was used only for a short time in chemical warfare, and most subjects studied were exposed to multiple war gases.[12] More recent series describe an initial obstructive defect, often with partial reversibility[3,13,14], restrictive defects with accompanying diffusion abnormalities have also been reported.[7,14] These initial changes reverted to normal within a few months in almost all patients studied. In fact, in a study involving 820 patients, Jones[15] found no radiologic or clinical evidence of permanent pulmonary damage following industrial chloride exposure. Lawson[16] also found no long-term residual changes in laboratory parameters, chest roentgenographic findings, or pulmonary function test results in over 457 cases of acute industrial chlorine gas exposure. In contrast, Kaufman and Burkons[17] found persistent obstructive lung disease up to 14 months following chronic chlorine exposure, and Kowitz et al[5] found persistent residual restrictive disease and low diffusing capacities up to 3 years following acute chlorine exposure. In another study, Jones et al[18] found that long-term sequelae after acute chlorine gas exposure were affected more by cigarette smoking than by the

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chlorine gas exposure. Other authors[3] have suggested that preexisting lung conditions do not affect the occurrence of pulmonary sequelae following chlorine gas exposure.

Our patient was exposed to chlorine gas in an industrial setting. Although the patient had a history of cigarette smoking and childhood asthma, he had had no symptoms of reactive airways disease for 20 years prior to this event. Following the chlorine exposure, the patient's symptoms rapidly became severely debilitating, necessitating daily therapy with high-dose corticosteroids, frequent use of home oxygen, and self-administered subcutaneous epinephrine.

To our knowledge, this case is unique in the literature. Charan et al[3] showed reversible acute airway obstruction shortly after exposure, and Hasan et al[13] reported the cases of two asthmatic patients in whom chlorine gas may have exacerbated a state of underlying hyperactivity. No one, however, has reported new onset of severe reversible airway obstruction that persisted several years after chlorine gas exposure. Thus, we believe that our patient represents a unique case of persistently debilitating asthma following acute chlorine gas exposure.

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Case Studies in Environmental Medicine

4

Chromium Toxicity

Environmental ALERT . . .

☑ *Chromium (III) is an essential nutrient, which can be toxic in large doses.*

☑ *The toxicity of chromium compounds depends on the oxidation state of the metal.*

☑ *Occupational exposure to chromium (VI) has been associated with increased incidence of lung cancer.*

☑ *The efficacy of chelation therapy in chromium poisoning has not been proven.*

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. The Agency for Toxic Substances and Disease Registry (ATSDR) and the Centers for Disease Control (CDC) designate this continuing medical education activity for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association and 0.1 continuing education units for other health professionals. See pages 21 to 23 for further information.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

Chronic skin ulcers and respiratory irritation in a 35-year-old handyman

A 35-year-old man is seen at your family practice office near a large Midwestern city with complaints of "allergies" and sores on his hands and arms. Over the past 2 to 3 months, the patient has noticed the onset of "runny nose," "sinus drainage," dry cough, and occasional nosebleeds (both nares intermittently). There is no prior history of allergies. He has also had occasional nausea and is concerned because the sores and minor skin cuts on his hands do not seem to heal. The patient denies having fever, chills, dyspnea, or change in bowel or bladder habits, and he has not noticed excessive thirst or easy bruising. He recently began experiencing loss of appetite and weight loss without dieting.

With the exception of the complaints mentioned, review of systems is otherwise unremarkable. The patient has used various over-the-counter remedies for his respiratory problems without relief. He did, however, note significant improvement in symptoms when he visited his sister in Chicago for 5 weeks at the end of summer.

Medical history reveals only usual childhood diseases. Other than OTC decongestants, he is taking no medications. He denies use of illicit drugs, but admits to occasional social use of alcohol. For the last 16 years he has smoked 1 pack of low-tar cigarettes a day.

The patient has been employed as a mathematics teacher for 13 years; summers are usually spent in self-employment as a handyman. His hobbies include reading and tennis. Two years ago he moved into a ranch-style house located several hundred yards from a small manufacturing plant; a small pond intervenes. The home has central air conditioning and gas heat; it is supplied with well water and uses a septic sewage system. Four months ago the patient began digging up the sewage system to make repairs. It was shortly after he began digging that he first noticed the sores on his hands and forearms.

Physical examination reveals an alert white male with skin lesions on the exposed areas of the forearms and hands; edema of the hands is present. The dermal lesions include dermatitis and small circular areas with shallow ulcerated centers. ENT examination is unremarkable, and chest examination reveals a few scattered rhonchi that clear with coughing. His liver is slightly enlarged and tender to palpation. Cardiovascular, genito-urinary, rectal, and neurologic examinations are unremarkable.

Initial laboratory findings include evidence of 2+ proteinuria and hematuria, and slightly elevated bilirubin, SGOT (AST), and SGPT (ALT). Scrapings of the dermal lesions, done with potassium hydroxide (KOH) preparation, show no fungal elements or signs of infestation on microscopic examination. A nasal smear for eosinophils is within normal limits.

Pretest

(a) Formulate an active problem list for this patient.

(b) What clues indicate this case may have an environmental etiology?

(c) What further information will you seek before making a diagnosis?

(d) What treatment will you recommend?

Answers to the Pretest can be found on page 19.

Exposure Pathways

- **Chromium exists in three common stable valence states; in order of generally increasing toxicity, they are chromium (0), (III), and (VI).**
- **Chromium is released to air primarily by combustion processes and metallurgical industries.**
- **Nonoccupational sources of chromium include contaminated soil, air, and water.**

Chromium is a hard, steel-gray metal highly resistant to oxidation even at high temperatures. It is the sixth most abundant element in the earth's crust, where it is combined with iron and oxygen in the form of chromite ore. The Soviet Union, South Africa, Albania, and Zimbabwe together account for 75% of world chromite production. Chromite ore has not been mined in the United States since 1961; in 1985 this country became completely dependent on importation for its primary chromium supply.

Chromium is used in three basic industries: metallurgical, chemical, and refractory (heat-resistant applications). In the metallurgical industry, chromium is an important component of stainless steels and various metal alloys. Metal joint prostheses made of chromium alloys are widely employed in clinical orthopedics. In the chemical industry, chromium is used primarily in paint pigments (chromium compounds can be red, yellow, orange, and green), chrome plating, leather tanning, and wood treatment. Smaller amounts are used in drilling muds, water treatment, catalysts, safety matches, copy machine toners, corrosion inhibitors, photographic chemicals, and magnetic tapes. Refractory uses of chromium include magnesite-chrome firebrick for metallurgical furnace linings and granular chromite for various other heat-resistant applications.

Chromium exists in a series of oxidation states from -2 valence to +6; the most important stable states are 0 (elemental metal), +3 (trivalent), and +6 (hexavalent). Chromium in chromite ore is in the trivalent state, whereas industrial processes also produce the elemental metal and hexavalent chromium. The health effects of chromium are at least partially related to the valence state of the metal at the time of exposure. Trivalent (Cr [III]) and hexavalent (Cr [VI]) compounds are thought to be the most biologically significant. Cr (III) is an essential dietary mineral in low doses, whereas certain compounds of Cr (VI) appear to be carcinogenic. Insufficient evidence exists to determine if Cr (III) or chromium metal can be human carcinogens.

Cr (III) and Cr (VI) are released to the environment primarily from stationary point sources resulting from human activities. Of the total atmospheric chromium emissions in the United States, approximately 64% is due to chromium (III) from fuel combustion (residential, commercial, and industrial) and from steel production; about 32% is due to chromium (VI) from chemical manufacture, chrome plating, and industrial cooling towers using chromate chemicals as rust inhibitors. A recent U.S. Environmental Protection Agency (EPA) report estimates that in the United States about 2840 metric tons of total chromium are emitted annually into the atmosphere (compared to approximately 110,000 tons of chromium metal produced each year).

Electroplating, leather tanning, and textile industries release relatively large amounts of chromium in surface waters. Solid wastes from chromate-processing facilities, when disposed of improperly in landfills, can be sources of contamination for groundwater, where the chromium residence time may be several years. The content of chromium in tap water in U.S. households is from 0.4 to 8.0 micrograms per liter (µg/L), which is slightly increased through use of stainless steel plumbing materials. (EPA's maximum contaminant level for chromium in drinking water is currently 50 µg/L.)

In the 1960s and 1970s, chromium-containing slag was used as landfill in residential, commercial, and recreational settings in over 100 locations in Hudson County, New Jersey. This fill contains chromium in carcinogenic forms and in concentrations acutely toxic in certain circumstances. Community exposure from this fill occurs in a variety of ways. Wind erosion of the soil can make slag particles airborne, increasing the opportunity for inhalation of chromium, and chromium compounds leached by rainwater have been found to migrate through cracks in soil, asphalt roadways, and masonry walls, forming high-content chromium crystals on their surfaces. In soil and roadways, these particles may be eroded by wind and foot traffic and carried as chromium-laden dust into homes and workplaces. Children playing in areas where the slag was used as fill may also be exposed through skin contact with chromium-contaminated dust, dirt, and puddles.

Less significant environmental sources of chromium include road dust contaminated by emissions of chromium-based catalytic converters or erosion products of asbestos brake linings, cement dust, tobacco smoke, and foodstuffs. Cigarettes contain 0.24 to 14.6 milligram chromium/kilogram, but neither the amount of chromium inhaled nor the chemical form is known. Processing and refining removes much of the normally small amount of chromium naturally present in foods.

Environmental and occupational sources of chromium exposure include the following:

Environmental	**Occupational**
Airborne emissions from	Welding of
• chemical plants	• alloys
• incineration facilities	• steel
Effluents from chemical plants	Leather tanning (soluble Cr [III])
Contaminated landfill	Chrome electroplating (soluble Cr [VI])
Cement dust	Chrome alloy production
Road dust from	Textile manufacturing
• catalytic converter erosion	Paints/Pigments (insoluble Cr [VI])
• asbestos brake lining erosion	Photoengraving
Tobacco smoke	Copier servicing

Challenge

(1) *On further questioning, the patient described in the case study relates that when he had reached several feet in depth while digging to repair the sewage system, he noticed an oozing from the ground of sometimes yellowish, sometimes greenish, water; this persisted throughout the several weeks of digging. The nearby pond, which is murky, also has a generally yellow tint with small areas of greenish color at times. Suspecting an environmental link, you contact the local health department. Extremely high levels of chromium are found in the pond water, and the investigators inform you that the nearby plant is electroplating auto parts with chromium.*

Discuss all sources and pathways by which this patient may be exposed to chromium.

Who's at Risk

- ☐ **Workers in industries producing and using chromium are at greatest risk of chromium's adverse effects.**
- ☐ **Risk assessment is currently underway for residents living on landfill derived from chromium-containing solid wastes.**

Workers in industries using chromium, especially stainless steel welding, chromate production, chrome plating, and chrome pigment industries, where exposure is primarily to Cr (VI), are at increased risk of chromium's effects. An estimated 175,000 workers may be exposed to Cr (VI) in the workplace on a regular basis; the number is much greater if exposure to other valence states of chromium are also considered. In many occupations, exposure is to both Cr (III) and Cr (VI) as soluble and insoluble materials.

Residents near chromate production facilities may be exposed to higher-than-background levels of chromium (VI). There is also concern that residents whose homes have been built on landfill using slag from smelters or chromate-producing facilities may be exposed to chromium through inhalation and dermal contact. Groundwater contamination may increase exposure in persons using well water as a drinking water source.

Coal and oil combustion contribute an estimated 1723 metric tons of chromium per year in atmospheric emissions; however, only 0.2% of this chromium is Cr (VI). In contrast, chrome-plating sources are estimated to contribute 700 metric tons of chromium per year to atmospheric pollution, but 100% is believed to be Cr (VI).

Despite air and water contamination from industrial pollution, no adverse health effects have been documented in persons residing near chromium point sources or in persons drinking chromium-contaminated water.

Challenge

(2) Besides the patient, who in the case study may be at risk of chromium exposure?

Biologic Fate

The entry routes of chromium into the human body are inhalation, ingestion, and dermal absorption. Occupational exposure generally occurs through inhalation and dermal contact, while the general population is exposed most often by the oral route through chromium content in soil, food, and water.

Rates of chromium uptake from the gastrointestinal tract are relatively low and depend on a number of factors, including valence state (with Cr [VI] more readily absorbed than Cr [III]), the chemical form (with organic chromium more readily absorbed than inorganic chromium), the water solubility of the compound, and gastrointestinal transit time. In humans and animals, less than 1% of inorganic Cr (III) and about 10% of inorganic Cr (VI) is absorbed from the gut; the latter amount is slightly higher in a fasting state.

The percentage of chromium absorption from the lungs cannot be estimated. Data from a few animal experiments indicate that with equal solubility, Cr (VI) compounds are absorbed more readily than Cr (III) compounds, probably because Cr (VI) readily penetrates cell membranes. Data from volunteers and indirect evidence from

- ☐ **Cr (VI) is better absorbed from the lungs, gut, and skin than Cr (III).**
- ☐ **After absorption, Cr (VI) is reduced to Cr (III).**
- ☐ **The difference in bioavailability and bioactivity between Cr (III) and Cr (VI) may account for the differences in toxicity.**
- ☐ **Only Cr (III) is excreted, primarily in the urine.**

occupational studies indicate that absorption of certain Cr (VI) compounds can occur through intact skin.

After entering the body from an exogenous source, Cr (III) does not readily cross cell membranes, but binds directly to transferrin, an iron-transporting protein in the plasma. In contrast, Cr (VI) after absorption is rapidly taken up by erythrocytes and reduced to Cr (III) inside the cell. Regardless of the source, Cr (III) is widely distributed in the body and accounts for most of the chromium in plasma or tissues. The greatest uptake of Cr (III) as a protein complex is by bone marrow, lungs, lymph nodes, spleen, kidney, and liver. Autopsies reveal chromium levels in the lungs are consistently higher than levels in other organs.

Excretion of chromium occurs primarily via the urine with no major retention in organs. In humans, the kidney excretes about 60% of an absorbed Cr (VI) dose in the form of Cr (III) within 8 hours of ingestion. Approximately 10% of an absorbed dose is eliminated by biliary excretion, and smaller amounts are excreted in hair, nails, milk, and sweat. Clearance from plasma is generally rapid (within hours), while elimination from tissues is slower (half-life of several days). In volunteers, administered doses of Cr (VI) were more rapidly eliminated than those of Cr (III).

Challenge

(3) Analysis of blood and urine specimens from the patient described in the case study reveals an elevated Cr (III) serum and urine concentration. Assuming the patient was exposed only to chromium (VI), explain the presence of chromium (III) in each of these body fluids.

Physiologic Effects

Chromium (III), an essential dietary element, plays a role in maintaining normal metabolism of glucose, fat, and cholesterol. Chromium's nutritional role has not been thoroughly delineated, but it appears to potentiate insulin action, probably in the form of glucose tolerance factor (GTF). The estimated safe and adequate daily intake of chromium for adults is in the range of 50 to 200 micrograms a day, although data are insufficient to establish a recommended daily allowance.

Dietary chromium deficiency is relatively uncommon; most cases occur in persons with special problems such as total parenteral nutrition, diabetes, or malnutrition. Chromium deficiency is characterized by glucose intolerance, glycosuria, hypercholesterolemia, decreased longevity, decreased sperm counts, and impaired fertility. In one patient receiving total parenteral nutrition, a peripheral neuropathy was corrected after chromium supplementation.

Major factors governing the toxicity of chromium compounds are oxidation state and solubility. Chromium (VI) compounds, which are powerful oxidizing agents and, as such, tend to be irritating and corrosive, appear to be much more toxic systemically than chromium (III) compounds, given similar amounts and solubilities. Although mechanisms of biologic interaction are uncertain, this differing toxicity may be related to the ease with which Cr (VI) can pass through cell membranes and its subsequent intracellular reduction to reactive intermediates.

☐ **Cr (III) is an essential trace mineral in human nutrition.**

☐ **Because Cr (VI) is a powerful oxidizing agent, exposure can cause irritating and corrosive effects.**

☐ **The target organ of inhaled chromium is the lung; the kidneys, liver, skin, and immune system may also be affected.**

Skin Effects

Chromic acid, dichromates, and other Cr (VI) compounds are not only powerful skin irritants but can also be corrosive. On broken skin, a penetrating round ulcer may develop. Common sites for these persistent ulcers ("chrome holes") include the nail root, knuckles and finger webs, back of the hands, and forearms. The characteristic chrome sore begins as a papule, forming an ulcer with raised hard edges. Ulcers may penetrate deep into soft tissue or become the site of secondary infection, but are not known to lead to malignancy. The progression to ulceration is generally painless, suggesting toxicity to peripheral sensory nerves. The lesions heal slowly and may persist for months.

☐ **Severe dermatitis and skin ulcers can result from contact with Cr (VI) salts.**

☐ **Chromium compounds can be sensitizers as well as irritants.**

At concentrations below those resulting in irritation, skin sensitivity is the most common effect after exposure to chromium compounds, especially Cr (VI) compounds. Up to 20% of chromium workers develop dermatitis. Allergic dermatitis with eczema has been reported in printers, cement workers, metal workers, painters, and leather tanners. Data suggest that a Cr (III)-protein complex is responsible for the allergic reaction, with Cr (III) acting as the hapten.

Respiratory Tract Effects

☐ **When inhaled, chromium (VI) is a respiratory tract irritant and may cause pulmonary sensitization.**

☐ **Chronic chromium inhalation increases the risk of lung cancer.**

Human occupational experience clearly indicates that, when inhaled, chromium (VI) is a respiratory tract irritant, resulting in airway irritation, airway obstruction, and possibly lung cancer. Dose, exposure duration, and the specific compound involved determine chromium's effects.

Pulmonary irritant effects after prolonged inhalation of chromate (VI) dust may include chronic irritation, congestion and hyperemia, chronic rhinitis, polyps of the upper respiratory tract, tracheobronchitis, and chronic pharyngitis. X-ray abnormalities reflect enlargement of the hilar region and lymph nodes, increased peribronchial and perivascular lung markings, and adhesions of the diaphragm. Consistent associations have been found between employment in the primary chromium industries and the risk for respiratory cancer (see Carcinogenic Effects section).

Pulmonary sensitization resulting in an asthmatic response is more common from Cr (VI) than from Cr (III). A delayed anaphylactoid reaction was reported in a male worker occupationally exposed to chromium vapors from chromium (VI) trioxide baths and chromium fumes from steel welding. A subsequent inhalation challenge with sodium chromate resulted in a reaction including late onset urticaria, angioedema, and bronchospasm accompanied by tripling of plasma histamine levels.

Many cases of nasal mucosa injury (inflamed mucosa, ulcerated septum, perforated septum) have been reported in workers exposed to Cr (VI) in chrome-plating plants and tanneries. A 1983 study of 43 chrome-plating plants in Sweden, where workers were exposed almost exclusively to chromic (VI) acid, revealed that all workers with nasal mucosa ulceration or perforation were periodically exposed to at least 20 $\mu g/m^3$ when working near the plating baths. (The current U.S. permissible exposure level in the workplace for chromates and chromic acid is 100 $\mu g/m^3$ over an 8-hour period.) The period of exposure for workers experiencing nasal mucosal ulceration varied from 5 months to 10 years.

Renal Effects

Studies of welders and chromium platers have found that workers with higher levels of exposure to airborne chromium (typically greater than 20 µg/m^3) show damage to renal tubules. Adverse renal effects have been reported in humans after inhalation, ingestion, and dermal exposure to chromium. Renal effects in animals occurred only after parenteral administration of large doses.

☐ **Low-dose, chronic chromium exposures generally cause only transient renal effects.**

☐ **Acute Cr (VI) exposure may result in renal tubular necrosis.**

Although glomerular injury has been noted in chromium workers, the predominant renal injury is tubular, with low doses acting specifically on the proximal convoluted tubules. Low-dose, chronic chromium exposure typically results only in transient renal effects. Elevated urinary β_2-microglobulin levels (an indicator of renal tubular damage) have been found in chrome platers, and higher levels generally have been observed in younger persons exposed to higher Cr (VI) concentrations. However, in a study of tannery workers (Cr [III] exposure) whose duration of employment ranged from 1 month to 30 years, urinary β_2-microglobulin levels were within normal limits, even though urinary chromium levels clearly indicated chromium exposure. A suggested urinary threshold for nephrotoxic effects is 15 µg chromium/g creatinine.

Hepatic Effects

Acute chromium exposure can result in hepatic necrosis. External chromic acid burns over 20% of a worker's body resulted in severe liver damage and acute renal failure. Limited data indicate that chronic inhalation of chromium compounds also can cause hepatic effects. Acute hepatitis with jaundice was reported in a woman who had been employed for 5 years at a chromium-plating factory. Tests revealed large amounts of urinary chromium, and liver biopsy showed abnormalities. Three coworkers exposed to chromic acid mists from the plating baths for 1 to 4 years also had mild to moderate liver abnormalities, as determined by liver function tests and liver biopsies.

☐ **Chromium (VI) may cause mild to moderate liver abnormalities.**

Carcinogenic Effects

Epidemiologic studies of occupational cohorts exposed to chromium aerosols provide clear evidence of carcinogenicity. In one key epidemiologic study involving workers at a chromate production plant who had worked for more than 1 year from 1931 to 1949, the percentage of deaths due to lung cancer was 18.2%; 1.2% was expected. For the 322 workers first employed from 1931 to 1937, the percentage of deaths due to lung cancer was close to 60%, with a latency period of approximately 30 years. Studies of workers in the chromium pigment, chrome-plating, and ferrochromium industries

☐ **Occupational exposure to Cr (VI) has long been associated with increased lung cancer mortality.**

☐ **Latency for chromium-induced lung cancer is greater than 20 years; exposure duration may be as short as 2 years.**

also suggest a statistically significant association between worker exposure to chromium and lung cancer. Increased lung cancer mortality has been associated with occupational exposures as short as two or three years. On the basis of these and other studies, EPA and the International Agency for Research on Cancer (IARC) have classified inhaled chromium (VI) as a known human carcinogen. Chromium (III) has not been classified as a human carcinogen by the National Toxicology Program, EPA, or IARC.

Although epidemiologic evidence strongly points to the hexavalent form of chromium as the agent in carcinogenesis, solubility and other characteristics of chromium compounds may be important in determining cancer risk. Data from animal studies do not resolve the issues of identities and potencies of various chromium-containing compounds as respiratory carcinogens. No chromium compound has been unequivocally shown to cause a significant increase in the number of neoplasms in experimental animals after exposure by natural routes (inhalation, ingestion, or dermal absorption), unless the animals were exposed until dead. (Standard protocols for animal experiments involve termination after 24 months.) However, intratracheal instillation, intrabronchial implantation, or injection of various chromium-containing compounds have produced tumors at the site of application in some cases.

No cancers, other than lung cancer, are associated with occupational chromium exposure. All pathologic cell types have occurred in chromium-induced lung cancers; however, small cell and poorly differentiated cancers predominate. Findings of some epidemiologic studies and animal experiments suggest chromium is also associated with nonrespiratory cancers, but the evidence is insufficient to consider the nonrespiratory cancers to be of a causal nature.

Reproductive and Developmental Effects

- ☐ **Data indicate chromium is teratogenic in animals.**
- ☐ **Potential reproductive effects of chromium in humans have not been adequately investigated.**

Chromium (III) is an essential element that is transported to the developing fetus. Less than 0.5% of Cr (III) was found to cross the placenta in mice when the chromium was administered as an inorganic salt, but 20% to 25% was found in litters when chromium was administered in a biologically active form, brewer's yeast. Adverse developmental effects in animals include cleft palate, hydrocephalus, delayed ossification, edema, and incomplete neural tube closure. Data are unavailable implicating chromium in adverse human reproductive or developmental effects.

Challenge

(4) *Could chromium toxicity account for the symptoms experienced by the patient described in the case study? Explain.*

(5) *Is the patient at increased risk of chromium-induced lung cancer?*

Clinical Evaluation

History and Physical Examination

Often there are no clear diagnostic clues in chromium-poisoned patients. A thorough history is therefore critical in evaluating a potentially exposed person. The patient's recent activities are important when health effects other than cancer are the major concern. Occupation, location of residence and workplace in relation to industrial facilities or hazardous waste sites, and source of drinking water supply should be investigated. In patients with known chronic chromium exposure, the physical examination should include evaluation of the respiratory system (if inhalation is involved), kidneys, liver, and skin.

☐ **If chromium exposure is suspected, the respiratory system, kidneys, liver, and skin should be evaluated.**

Signs and Symptoms

Acute Exposure

- ☐ **Ingestion of a lethal dose of chromate may result in cardiovascular collapse due to severe hypovolemia.**
- ☐ **Sublethal doses of chromate may lead to renal and hepatic necrosis 1 to 4 days after ingestion.**

Severe exposures to chromium compounds are rarely occupational or environmental, but are usually accidental or suicidal. Short-term, high-level exposure to Cr (VI) produces irritation at the site of contact including ulcers of the skin, irritation of the nasal mucosa, perforation of the nasal septum, and irritation of the gastrointestinal tract. Less is known about the acute toxicity of Cr (III) compounds, although they are generally believed to be less toxic.

About 1 gram of potassium dichromate (IV) is considered a lethal dose. Persons who ingested 5 grams or more experienced gastrointestinal bleeding, massive fluid loss, and death within 12 hours after ingestion. When the ingested dose was 2 grams or less, renal tubular necrosis and diffuse hepatic necrosis resulted and contributed to death in some cases. Typically, the kidney and liver effects develop 1 to 4 days after ingestion of a sublethal dose. Other symptoms of acute Cr (VI) ingestion include vertigo, thirst, abdominal pain, and vomiting. Oliguria, anuria, shock, convulsions, coma, and death can ensue. Gastrointestinal hemorrhage and coagulopathy may also occur. Acute chromium poisonings are often fatal regardless of the therapy employed.

Dermal contact with Cr (VI) compounds can result in severe systemic toxicity. Antiscabies ointment containing Cr (VI) resulted in necrosis of skin at application sites, nausea, vomiting, shock, coma, and death. In one case, severe nephritis and death followed cauterization of an open wound with chromium (VI) oxide, and an occupational fatality was described after an accident in which a worker was burned on the arms and trunk with hot potassium dichromate. Both of these cases involved broken rather than intact skin.

Chronic Exposure

- ☐ **In occupational settings, the most commonly reported effects of chronic chromium exposure are contact dermatitis, and irritation and ulceration of the nasal mucosa.**
- ☐ **Less common are reports of hepatic and renal damage and pulmonary effects.**
- ☐ **Lung cancer is a potential long-term effect of chronic Cr (VI) exposure.**

Repeated skin contact with chromium dusts may lead to incapacitating eczematous dermatitis with edema. Chromate dusts may also produce irritation of the conjunctiva and mucous membranes, as well as nasal ulcers and perforations. When a solution of chromate contacts the skin, it can produce penetrating lesions known as chrome holes or chrome ulcers, particularly in areas where a break in the epidermis is already present. These ulcers are usually painless but may persist for months. Acute hepatitis with jaundice has also been observed in workers chronically exposed to Cr (VI). Lung cancer is the most serious long-term effect.

Low-level environmental exposures have not resulted in adverse effects in human populations. Long-term studies in which animals have been exposed to low levels of chromium in food or water have produced no harmful effects.

Laboratory Tests

A general medical workup for a patient with suspected chronic chromium exposure might include the following:

- Screening Tests
  - Complete blood count
  - Blood panel
  - Liver function tests (SGOT or AST, SGPT or ALT, and bilirubin)
  - BUN and creatinine
  - Urinalysis
- Specialized Tests
  - Blood and urine chromium levels
  - β_2-microglobulin

If chromium inhalation has occurred, a chest X ray, pulmonary function testing, and a nasal smear for eosinophils should be included.

Direct Biologic Indicators

When obtaining biologic specimens for chromium analysis, care must be taken to avoid sample contamination and chromium loss during collection, transportation, and storage. For example, use of stainless steel utensils to collect tissue samples may raise tissue chromium levels, as will stainless steel grinding and homogenizing equipment. Some plastic containers contain significant amounts of leachable chromium; therefore, specially prepared acid-washed containers should be obtained from the laboratory. Considerable care also must be taken in the analysis to minimize chromium volatilization during sample ashing.

☐ **Chromium can be measured in blood and urine; hair or nail analysis has no clinical value.**

☐ **The correlation between exposure levels and urinary chromium excretion is useful in occupational settings.**

Another difficulty in the available techniques is the inability to distinguish between Cr (III) and Cr (VI). This is particularly important in environmental samples since Cr (VI) has been associated with serious health hazards, whereas Cr (III) is of far less concern.

Blood or serum chromium levels. Blood distribution of chromium appears to be divided evenly between plasma and erythrocytes. In the absence of known exposure, whole blood chromium concentrations are in the range of 2.0 to 3.0 µg/100 mL; lower levels are seen in rural areas, and higher levels occur in large urban centers. Values above background levels are considered potentially toxic, but levels have not been correlated with specific physiologic effects. Chromium rapidly clears from the blood, and measurements relate only to recent exposure.

Urinary chromium levels. Wide individual variation in metabolism and rapid depletion of body burden limit the value of urinary chromium monitoring. Urinary chromium excretion reflects absorption over the previous 1 or 2 days only. If sufficient time has elapsed for urinary clearance, a negative biomonitoring result can occur even with injurious past exposure. Assuming no source of excessive exposure, urinary chromium values are typically less than 10 µg for a twenty-four-hour period.

In occupational settings, a urinary chromium concentration of 40 to 50 µg/L immediately after a workshift reflects exposure to air levels of 50 µg/m^3 of soluble Cr (VI) compounds, a concentration associated with nasal perforations in some studies. The American Conference of Governmental Industrial Hygienists (ACGIH) intends to recommend a workplace biologic exposure index (BEI) for total urinary chromium as follows: no more than 10 µg chromium/g creatinine increase during a work shift, and a urinary value of less than 30 µg chromium/g creatinine at the end of the work week.

Chromium levels in hair and nails. Hair or nail analysis is of little use in evaluating an individual patient since it is impossible to distinguish chromium bound within the hair during protein synthesis from chromium deposited on the hair from dust, water, or other external sources. Populations with no known chromium exposure reportedly have hair levels ranging from 50 to 1000 ppm chromium.

Challenge

(6) Analysis of the tap water in the patient's home reveals a greenish tinge and a chromium concentration of 746 µg/L. Your diagnosis is chromium toxicity. Are there any other tests the patient should undergo?

(7) The patient described in the case study insists on obtaining a hair analysis. The chromium content of the hair sample is 1038 ppm. How will you interpret this result?

Treatment and Management

Acute Exposure

Treatment in cases of acute, high-level chromium exposure is usually supportive and symptomatic. Supportive measures may include ventilatory support, cardiovascular support, and monitoring for renal and hepatic function. When renal function is compromised, urine alkalinization and maintenance of adequate urine flow are important. Progression to anuria is associated with poor prognosis.

If the eyes and skin are directly exposed, flush with copious amounts of water. Topical ascorbic acid has been successfully used to prevent chromium dermatitis and dermal burns caused by dichromate.

Gastric lavage with magnesium hydroxide or another antacid may be useful in cases of chromium ingestion. Fluid and electrolyte balance is critical. The efficacy of activated charcoal has not been proven. Hemodialysis, exchange transfusions, or chelating agents such as BAL (dimercaprol) or EDTA (ethylenediaminetetraacetic acid) have not been shown to be effective in the treatment of human poisoning. Orally administered ascorbic acid was found to be protective in experimental animals and was reported beneficial in at least one patient after chromium ingestion.

- ☐ **No proven antidote is available for chromium poisoning.**
- ☐ **Acute poisonings are often fatal regardless of therapy.**

Chronic Exposure

In most patients with chronic, low-dose exposure, no specific treatment is needed. The mainstay of management is removing the patient from further exposure and relying on the urinary and fecal clearance of the body burden. Although normal urinary excretion is quite rapid, forced diuresis has been used. Except in the lungs, only small amounts of chromium are retained several weeks after exposure has ceased. Dermatitis and liver and renal injury will not progress after removal from exposure and, in most cases, the patient will recover. Weeping dermatitis can be treated with 1% aluminum acetate wet dressings, and chrome ulcers can be treated with topical ascorbic acid.

If the exposure has been lengthy (i.e., 2 to 3 years), the increased risk of lung cancer should be discussed with the patient. Although no reliable tests are currently available to screen patients for lung cancer, the physician can intervene with advice and education in smoking cessation, exposure to other known pulmonary carcinogens, and in general, preventive health education. Annual chest X rays may be advisable in carefully selected cases.

- ☐ **Treatment consists of removal of the patient from further chromium exposure, reliance on the body's naturally rapid clearance of the metal, and symptomatic management.**

Challenge

(8) What is the recommended treatment for the patient described in the case study?

Standards and Regulations

Table 1 summarizes the U.S. standards and regulations for chromium salts, which are discussed in more detail below.

The Workplace

Air

☐ **OSHA mandates an 8-hour time-weighted average of 100 µg/m³ for chromic acid and chromates.**

In 1985, the Occupational Safety and Health Administration (OSHA) mandated an 8-hour workday, 40-hour workweek permissible exposure limit (PEL) of 100 µg CrO_3/m^3 for chromic acid and chromates (ceiling). For soluble Cr (VI) salts the PEL is an 8-hour time-weighted average (TWA) of 500 µg Cr/m^3. For chromium metal and for insoluble salts the TWA is 1000 µg Cr/m^3.

NIOSH's recommended exposure limit is a 10-hour TWA for carcinogenic Cr (VI) compounds of 1 µg Cr (VI)/m³. For noncarcinogenic Cr (VI) compounds (a category which includes chromic acid), the recommended exposure limit is 25 µg Cr (VI)/m³ as a 10-hour TWA and a 15-minute ceiling of 50 µg Cr (VI)/m³. Based on current evidence, NIOSH considers the noncarcinogenic Cr (VI) compounds to be the mono- and dichromates of hydrogen, lithium, sodium, potassium, rubidium, cesium, and ammonia, and chromic acid anhydride. Carcinogenic Cr (VI) compounds comprise any and all Cr (VI) materials not mentioned in the noncarcinogenic group above.

Environment

Air

EPA does not have an emission standard for chromium and, therefore, does not regulate chromium levels in ambient air.

☐ **No federal emission standard currently exists for chromium.**

Drinking Water

EPA has a current enforceable standard of 50 µg/L (50 ppb) total chromium in drinking water. In May 1989, EPA recommended a maximum contaminant level (MCL) of total chromium in drinking water of 100 µg/L (100 ppb). Action on the proposed standard has received public comment, and action will likely be taken by EPA in December 1990.

☐ **The current maximum contaminant level for chromium in drinking water is 50 µg/L.**

Table 1. Standards and regulations for chromium

Agency[*]	Focus	Level	Comments
ACGIH	Air Workplace	50 $\mu g/m^3$	Advisory, TWA[†] to avoid carcinogenic risk from certain insoluble chromium compounds
NIOSH	Air Workplace	1 $\mu g/m^3$	Advisory; TWA[†] (10-hour) for carcinogenic Cr (VI) salts
		25 $\mu g/m^3$	TWA[†] (10-hour) for noncarcinogenic Cr (VI) salts, including chromic acid
		50 $\mu g/m^3$	15-minute ceiling limit for noncarcinogenic Cr (VI) salts
OSHA	Air Workplace	100 $\mu g/m^3$	Regulation, PEL[§] for chromic acid and chromates (ceiling)
		500 $\mu g/m^3$	PEL[§] for soluble chromic salts (8-hour TWA[†])
		1000 $\mu g/m^3$	PEL for chromium metal and insoluble salts (8-hour TWA[†])
EPA	Air-Environment	N/A	Under review
	Drinking Water	50 µg/L	Regulation, current MCL[¶] for total chromium, proposed MCL is 100 µg/L

[*] ACGIH = American Conference of Governmental Industrial Hygienists, EPA = Environmental Protection Agency; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration

[†] TWA (Time-Weighted Average) = time-weighted average concentration for a normal workday and 40-hour workweek to which nearly all workers may be repeatedly exposed

[§] PEL (Permissible Exposure Limit) = an allowable exposure level in workplace air

[¶] MCL (Maximum Contaminant Level) = enforceable standard for drinking water

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Environmental Protection Agency. Health effects assessment for trivalent chromium. Cincinnati, OH: Environmental Protection Agency, Environmental and Criteria Assessment Office, 1984. EPA report no. 540/1-86-035.

Answers to Pretest and Challenge Questions

Pretest

The Pretest can be found on page 1.

(a) A problem list for this patient would include the following:
  - upper and lower respiratory irritation
  - multiple skin lesions and edema of the hands
  - loss of appetite and weight loss
  - liver and renal dysfunction
  - cigarette smoking

(b) Information suggesting an environmental etiology includes the following: onset of the patient's symptoms coincide with activity outside the usual routine; the patient mentions he first noticed the sores on his hands and forearms while digging up the sewage system to make repairs. Another clue to a possible environmental cause is temporary relief of symptoms when the patient leaves his usual habitus, as occurred when he visited Chicago. Proximity of the patient's home to an industrial facility (i.e., the electroplating plant) is also an important clue.

(c) You may identify possible causes for the dermal lesions by consulting a dermatologist. The cause of the persistent (2 to 3 months) respiratory symptoms that do not respond to OTC decongestants in a person with no history of allergies should be pursued; the patient should be queried about whether the onset of symptoms coincided with the move to his home, whether odors have emanated from the plant, etc. More information regarding the patient's observations and activities while digging up the sewage system also may be helpful.

(d) See answer to Challenge question 8.

Challenge

Challenge questions begin on page 4.

(1) The most important pathways for possible chromium exposure in this case are dermal contact during the unearthing of the sewage system; inhalation of emissions from the plant or soil particles if the pond dries up; and ingestion, if the drinking water has been contaminated by effluents from the plant.

Minor sources (inhalation) of chromium may be road and cement dust, erosion products of brake linings and emissions from automotive catalytic converters, and tobacco smoke. Cigarettes contain 0.24 to 14.6 mg/kg chromium, although it is not known how much of this is inhaled. Foodstuffs (ingestion) generally contain extremely low chromium levels.

(2) If effluent from the plant has reached the groundwater, community residents who drink well water may be at risk. Airborne plant emissions may have also reached nearby residents. Workers at the plant who prepare the plating baths and work near them may be receiving significant exposure.

(3) Chromium (VI) is a powerful oxidizing agent. In the plasma and cells, it is readily reduced to chromium (III), which is excreted in the urine.

(4) Yes, persistent dermal ulcers, respiratory tract irritation, and pulmonary sensitization are all possible effects of chromium exposure.

(5) While it cannot be ruled out, it is unlikely that the dermal and inhalation chromium exposure of this patient will cause lung cancer. Persons who have developed lung cancer after chromium exposure were workers who had significant inhalation exposure for 2 years or longer. Because this patient's inhalation exposure is at ambient air levels and probably of 2 years duration at most, any increase in his relative risk would not be great.The patient should be advised to stop smoking cigarettes because smoking may act synergistically to increase risk and is itself a significant risk factor for lung cancer. The data is insufficient to estimate the risk from ingestion of the contaminated drinking water.

(6) If exposure was recent, chromium levels in blood or urine may be used to confirm exposure. Renal function should be tested (urinalysis, BUN, creatinine, and β_2-microglobulin) to determine if renal tubular damage has occurred.

(7) No useful interpretations can be drawn from the hair analysis. A result of 1038 ppm is beyond the range for unexposed persons (50 to 1000 ppm); however, the sample could have been environmentally contaminated with chromium from the water during bathing, or by chromium in ambient air polluted by the plant emissions. There are no standard methods for obtaining a hair sample nor for washing and preparing it for analysis, and these techniques can greatly influence results. Finally, there is no research that proves a correlation between chromium content of hair and exposure levels or physiologic effects; therefore, the result has no clinical significance.

(8) If the sources of chromium exposure can be eliminated for this patient, except for the skin lesions, no further treatment would be required. Topical ascorbic acid has been useful in the treatment of chrome ulcers and 1% aluminum acetate wet dressings can be used to treat the dermatitis.

This patient's case may be a sentinel for community exposure. You should contact the local health department, OSHA, and EPA to report your patient's adverse effects and discuss your suspicions of the chromium source. Chromium levels in and around the plant should be measured. If a hazard exists, workers should be provided proper protective gear, trained, and medically monitored. Since EPA does not currently have an emission standard, it may be difficult to abate the atmospheric source of chromium. Decontamination of the pond site may require regulatory action and litigation. Residents who use well water should be encouraged to use an alternate water source for drinking and cooking.

ATSDR November 1991
Case Studies in Environmental Medicine

15

Cyanide Toxicity

Environmental ALERT...

☑ *Cyanide is one of the most rapidly acting poisons.*

☑ *Cyanide poisoning is a hazard in many enclosed-space fires, and its occurrence in smoke-inhalation victims may be underestimated.*

☑ *Acute cyanide exposure results primarily in CNS, cardiovascular, and respiratory effects; thyroid function abnormalities also have been noted in persons chronically exposed.*

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. The Agency for Toxic Substances and Disease Registry (ATSDR) and the Centers for Disease Control (CDC) designate this continuing medical education activity for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association and 0.1 continuing education units for other health professionals. See pages 21 to 23 for further information.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

Hypotension and coma in a 5-year-old victim of smoke inhalation

You are alerted by paramedics who are en route to the emergency department. They will arrive within 10 minutes with two apparent smoke-inhalation victims: a young woman, approximate age 35, and her son, approximate age 5. Upon arrival at the scene, firefighters found both victims unconscious near the doorway; the entire house was smoke-filled. The fire, which was confined to the child's bedroom and two adjacent rooms, was started by a toy that the child poked into an electric space heater. It is probable that the woman was in another part of the house when the fire began and attempted to rescue the child but was overcome by the thick black smoke. Both victims are unconscious. The paramedics report no evidence of trauma or burns in either victim. The mother has nonpurposeful movements, but the child is flaccid and unresponsive to painful stimuli. Soot is present in the child's nose and throat.

En route to the hospital, IVs were started. The woman's vital signs include BP 70/50 mm Hg, pulse 120/min, respiration rate 30/min. She is being administered 100% oxygen via face mask. The child's vital signs include BP 50/20 mm Hg, pulse 50/min, respiration rate 0/min. He is intubated and mechanically ventilated, and is being administered supplemental oxygen.

Upon arrival at the hospital, the woman is improved but is lethargic and disoriented; the child is still unresponsive even to deep pain. Both victims have adequate pO_2 levels. The mother's initial carboxyhemoglobin level is 25%; the child's carboxyhemoglobin level is 40%. The child remains bradycardic and hypotensive.

The following day, having heard that cyanide may have played a role in the condition of these smoke-inhalation victims, a neighboring couple, who have recently learned that for 2 years they had been drinking well water containing 212 parts per billion (ppb) cyanide, are concerned that they may experience adverse health effects. They ask to be evaluated.

Pretest

(a) *What are the possible causes of coma in the fire victims?*

(b) *What laboratory tests would help to confirm the diagnosis?*

(c) *What treatment should be initiated immediately?*

(d) *What are the possible long-term sequelae for the fire victims and the neighbors who drank cyanide-containing well water?*

Answers can be found in Challenge answers (6) through (13) on pages 18-19.

Exposure Pathways

- ☐ **Many fruits and vegetables contain cyanide-generating substances.**
- ☐ **Cyanide contamination in air and water arises primarily from industrial pollution and vehicle exhaust.**
- ☐ **Cigarette smoke contains cyanide.**
- ☐ **Cyanide poisoning is an inhalation hazard in many enclosed-space fires.**

Cyanide is one of the most rapidly acting poisons known and accounts for many suicidal and homicidal deaths. Cyanide can exist in many forms. The most common are hydrogen cyanide (HCN) and cyanide salts (potassium cyanide, sodium cyanide, calcium cyanide), which can combine with acid to release HCN. A number of aliphatic nitrile compounds (i.e., acrylonitrile, acetonitrile, proprionitrile) and aliphatic thiocyanates can release cyanide by hepatic metabolism after absorption, resulting in delayed-onset cyanide poisoning. Children have developed symptoms of cyanide poisoning hours after drinking acetonitrile-based artificial nail remover.

Cyanide salts are generally colorless solids, whereas HCN, also known as prussic acid, is a colorless gas at room temperature. Because of its rapid action, HCN is employed in gas chamber executions in the United States and other countries. A cyanide salt was used in the Jonestown massacre, and potassium cyanide was responsible for the deaths of seven persons in the Chicago area who consumed intentionally tainted capsules of an over-the-counter pain reliever.

Cyanide compounds have a faint, bitter almond odor, detectable at a threshold of 0.2 to 5.0 parts per million (ppm). (The current permissible workplace short-term exposure limit [STEL] for hydrogen cyanide is 10 ppm.) The ability to smell cyanide is a genetically determined trait, which is absent in 20% to 40% of the population.

Cyanogenic glycosides, which occur naturally in a number of plants, release HCN after ingestion. In the United States, cyanide intake through food consumption is normally low since foods high in cyanogenic substances are not a major part of the American diet. However, eating large amounts of seeds, pits, and stone fruits of certain plants (or blending them in "milkshakes") reportedly has caused illness especially in children, and even death. As many as 1000 plants contain cyanogenic glycosides. The more common include the following:

apple (seeds)
bamboo (sprouts)
cassava (beans and roots)
Christmas berry
crab apple (seeds)
cycad nut
elderberry (leaves and shoots)
hydrangea (leaves and buds)
lima beans (black bean grown
  in tropical countries)
pear (seeds)

Prunus species (leaves, bark, seeds)
  apricot
  bitter almond
  cherry laurel
  chokecherry
  mountain mahogany
  peach
  pin cherry
  plum
  western chokeberry
  wild black cherry

Adapted from Kingsbury JM. *Poisonous Plants of the United States and Canada*. Englewood Cliffs, NJ: Prentice-Hall, 1964, p 26. Used by permission of Prentice-Hall.

Laetrile, a compound used for cancer treatment by some nontraditional practitioners, contains amygdalin, which releases cyanide when administered orally. Laetrile has been sanctioned in 22 states, despite lack of Federal Drug Administration (FDA) approval. No evidence of laetrile's efficacy exists, and several cases of serious and fatal cyanide poisonings have been reported. Sodium nitroprusside, $NaFe(CN)_5NO$, is an intravenous medication used in acute hypertensive crises. Its cyanide metabolite can reach toxic levels if the recommended dosage is exceeded, if infusion is prolonged or rapid, or if renal failure occurs. Phencyclidine (PCP), an illicit street drug, may contain cyanide if improperly manufactured.

For the general population, the single largest source of airborne cyanide exposure is vehicle exhaust. Vehicle emission rates can be reduced from 14 milligrams (mg) cyanide per mile to about 1 mg per mile by catalytic converters operating optimally. Other atmospheric sources include emissions from chemical processing industries, iron and steel mills, metallurgical industries, metal plating and finishing industries, petroleum refineries, municipal waste incinerators, and cigarette smoke.

Water sources can be contaminated with cyanide by industrial effluents, migration of cyanide from landfills, and to a lesser extent, by runoff from cyanide-containing salts used on roads. The largest sources of cyanide in water are discharges from organic chemical industries, iron and steel plants, and wastewater treatment works. A 1978 U.S. Environmental Protection Agency (EPA) survey of interstate drinking water supplies showed that about 7% of the samples had cyanide concentrations greater than 10 parts per billion (ppb). (The anticipated drinking water standard to be proposed by EPA in 1990 is 200 ppb.) Cyanide has been detected in some surface waters at concentrations above the level safe for aquatic life.

Virtually any substance containing both carbon and nitrogen can release cyanide when burned under certain conditions. HCN is released during pyrolysis of synthetic polymers containing nitrocellulose, acrylonitrile, or urea formaldehyde. Many common textiles, foam, and plastic materials in the home may be sources of HCN in a fire. Some natural products such as silk and wool can also release cyanide when burned.

Challenge

(1) Explain how the smoke-inhalation victims described in the case study could have been poisoned by cyanide.

(2) What additional information would you gather from the neighboring couple regarding their exposure to cyanide?

Who's at Risk

☐ **Workers have the greatest likelihood of exposure to high concentrations of cyanide.**

☐ **One lighted cigarette can produce 20 to 450 μg of cyanide, increasing the risk to smokers.**

☐ **The incidence of cyanide poisoning may be underestimated in smoke-inhalation victims.**

A 1981-1983 National Institute for Occupational Safety and Health (NIOSH) survey estimated that 143,720 workers in a wide variety of occupations were potentially exposed to cyanide compounds, including, but not limited to, the following:

- blacksmiths
- chemical laboratory workers
- electroplaters
- fumigant applicators
- manufacturers and users of plastics and paint (acrylates, methacrylates, nitriles)
- metallurgists
- metal cleaners
- photoengravers
- reclaimers of silver from photographic materials
- steel manufacturers
- tanners

Firefighters may be exposed to HCN generated during combustion of certain types of plastics, foams, and textiles. Effects due to occupational exposures are usually the result of inhalation.

Each pack of cigarettes smoked releases 250 to 10,000 micrograms (μg) of cyanide, much of which the smoker may inhale. Smokers generally have higher blood cyanide levels than nonsmokers and are at increased risk of cyanide's nervous system effects, particularly tobacco amblyopia and retrobulbar optic neuritis.

Significant blood cyanide levels have been reported in many fire-related smoke-inhalation victims. In one study of 52 fire fatalities, some victims had very high cyanide levels with relatively low carbon monoxide levels. Data suggest that the risk of cyanide intoxication in enclosed-space smoke inhalation injury is probably underestimated. HCN in the air can cause weakness and loss of muscle coordination, making escape from the area of a fire more difficult.

Challenge

(3) Both victims described in the case study were overcome in the same fire. Would you expect them to have similar blood cyanide levels? Explain.

(4) What are other possible causes of an elevated blood cyanide level?

Biologic Fate

Cyanide is absorbed through the lungs, GI tract, and skin. Symptoms can occur within seconds of HCN inhalation, within minutes after ingestion of cyanide salts, and onset may be delayed up to 12 hours after ingestion of cyanogenic glycosides, nitriles, or thiocyanates. Absorption time after ingestion depends on gut pH and solubility of the cyanide-containing compound. Cyanide is readily absorbed via the mucous membranes and eyes. Clinical cases of cyanide poisoning after dermal exposure are rare and most often have involved burns with molten cyanide salts or immersion in cyanide solutions.

Once cyanide is absorbed, it is rapidly distributed by the blood throughout the body. Cyanide exerts toxic effects by combining with the ferric (+3) iron in cytochrome oxidase, which inhibits cellular oxygen utilization. Blockade of the cytochrome oxidase system

- ☐ **Cyanide is absorbed by all routes.**
- ☐ **Cyanide causes cellular asphyxiation by inhibiting the cytochrome oxidase system.**

causes anaerobic metabolism with resultant lactate production and severe metabolic acidosis. Cyanide also inhibits other enzymes and can combine with certain metabolic intermediates.

Eighty percent of absorbed cyanide is detoxified in the liver by the mitochondrial enzyme rhodanese, which catalyzes the transfer of sulfur from a sulfate donor to cyanide, forming less toxic thiocyanate. Thiocyanate is readily excreted in urine. Other detoxification pathways exist, including reaction with hydroxocobalamin (vitamin B_{12a}) to form cyanocobalamin. A small amount of cyanide is eliminated as CO_2 in expired air, along with small amounts of HCN.

A number of compounds have been found to act synergistically with cyanide, producing toxic effects. Smoke-inhalation victims have experienced additive or synergistic effects from carbon monoxide and cyanide, and only recently has attention been focused on the potential for combined poisoning in victims of enclosed-space fires.

Physiologic Effects

☐ **The cardiovascular, respiratory, central nervous, and endocrine systems may be adversely affected in cyanide poisoning.**

Cyanide adversely affects the cardiovascular, respiratory, central nervous, and endocrine systems. It is unlikely that cyanides are carcinogenic. Epidemiologic studies indicate that cyanide may be teratogenic in humans, but data are scarce. Reproductive effects of cyanide in humans have not been studied.

There is great variability among "lethal doses" reported in the literature, probably due to differences in supportive care and therapy rendered. The potential lethal oral adult dose of cyanide salts in the absence of medical care is 200 to 300 mg, although persons ingesting 1 to 3 grams (g) of cyanide salts have survived. Inhaling 600 to 700 ppm hydrogen cyanide for 5 minutes or approximately 200 ppm for 30 minutes may be fatal. Survival in any specific case often depends upon the rapidity and scope of treatment.

Acute Exposure

☐ **The effects of acute cyanide exposure are dominated by CNS disturbances.**

☐ **Because of its high metabolic demands, the brain is particularly susceptible to cyanide poisoning.**

An acute cyanide exposure affects primarily the central nervous system, initially producing stimulation, which may be followed quickly by depression. Stimulation of peripheral chemoreceptors produces increased respiration, while stimulation of the carotid body receptors slows the heart rate. These early changes are often transient and may be followed by hypoventilation progressing to apnea and myocardial depression. The result is hypotension and shock, which are rapidly fatal if untreated. Because of the brain's susceptibility to cyanide, electrical activity may cease while the heart is still beating.

Predominance of anaerobic metabolism within a cyanide-poisoned cell induces a decrease in the ATP/ADP ratio and thus alters energy-dependent processes such as calcium homeostasis. Disruption in calcium regulation with resultant changes in neurotransmitter releases can alter the electrical activity in the brain and may be an important factor in the manifestation of cyanide-induced neurotoxic effects such as tremors and convulsions. Delayed onset Parkinson-like syndromes have been described after severe cyanide poisoning as well as after carbon monoxide poisoning, implying that the basal ganglia are sensitive to the neurotoxic effects of both agents.

Chronic Exposure

Central Nervous System

An epidemic of spastic paraparesis in Mozambique was attributed to consumption of the cyanogenic vegetable, cassava. Some members of the affected population developed neurologic abnormalities such as demyelination of peripheral nerves with decreased conduction velocity, optic neuropathy, and deafness. A variety of Parkinson-like signs were also present. However, diets deficient in vitamin B_{12} also can result in nerve cell destruction, even when large amounts of cyanogenic foods are not consumed.

☐ **Chronic degenerative neuropathy has been associated with cassava consumption in Mozambique.**

Inhalation of cyanide from tobacco by heavy smokers with poor diets has been associated with tobacco amblyopia, retrobulbar neuritis, and optic atrophy, characterized by a loss of visual acuity. Leber's hereditary optic atrophy is associated with a defective rhodanese-catalyzed metabolism of cyanide to thiocyanate. Quantitative data associating neurologic effects with long-term occupational cyanide exposures are limited.

Cardiovascular and Respiratory Effects

Although cyanide appears to affect vascular smooth muscle directly, effects on the respiratory and cardiovascular systems may be at least partially secondary to central nervous system effects. In acute poisoning, depression of the CNS respiratory centers causes hypoventilation leading to apnea. Direct myocardial depression, as well as hypoxemia from hypoventilation, leads to decreased cardiac output and hypotension.

☐ **Respiratory and cardiovascular effects of cyanide poisoning may be secondary to the CNS effects.**

Electrocardiographic abnormalities, palpitations, and chest pain have been noted in chronically exposed workers. Electroplaters who had been exposed to airborne cyanide concentrations of approximately 6 to 10 ppm for 5 to 15 years also complained of dyspnea on exertion.

Endocrine Effects

☐ **Thyrotoxicity has been linked with inhalation and ingestion of cyanide.**

One study of electroplaters revealed that over 50% had enlarged thyroid glands. Other studies of cyanide-exposed workers have noted mild subclinical abnormalities of thyroid function. Populations in which the cassava is a staple food show a strong correlation between cassava consumption and endemic goiter and cretinism. Thiocyanate, the detoxification product of cyanide, and dietary deficiencies such as low intake of iodine may play a role in producing these thyroid effects.

Developmental Effects

☐ **Data regarding cyanide's teratogenic effects on the human fetus are lacking.**

Cyanide and various cyanogenic compounds (laetrile, cassava powder, acetonitrile, proprionitrile, acrylonitrile) have produced a variety of teratogenic effects in animals, most of which can be prevented when the dams are administered a cyanide antidote, sodium thiosulfate. In humans, low birth weights have been noted in the children of women chronically exposed to cyanide.

Challenge

(5) What is the prognosis for each of the smoke-inhalation victims described in the case study?

Clinical Evaluation

History and Physical Examination

Pertinent history may include occupation and hobbies, medications, diet, smoking habits, and drinking water source. Physical examination of chronically exposed patients should include particular attention to neuropsychiatric and ophthalmologic examinations, and cardiovascular system and thyroid functioning.

Because cyanide can kill quickly, acute poisoning requires rapid intervention. Unfortunately, positive diagnosis is often difficult, especially when the history cannot be obtained. Knowledge of the patient's occupation, mental status before poisoning, probability of suicidal intent, or location at onset of symptoms can be vital in making a diagnosis.

Persistent acidosis or hypotension in a smoke-inhalation victim should raise the suspicion of concomitant cyanide poisoning. In an unresponsive victim, trauma should be ruled out by a thorough examination, which should be repeated frequently. When clinically indicated, confirmatory tests, such as peritoneal lavage for intraperitoneal hemorrhage and a CAT scan for intracranial injury, should be performed.

Signs and Symptoms

Acute Exposure

- ☐ **CNS and cardiovascular signs predominate in persons acutely exposed.**
- ☐ **Posthypoxic encephalopathy, Parkinson-like syndromes, and delayed posthypoxic myocardial lesions are sequelae of severe cyanide poisoning.**

Signs and symptoms of acute cyanide toxicity reflect cellular hypoxia and initially may be nonspecific, generalized, and nondiagnostic. With acute inhalation of HCN gas, death may occur within seconds.

Central nervous system symptoms include faintness, flushing, anxiety, excitement, perspiration, vertigo, headache, drowsiness, prostration, opisthotonos and trismus, hyperthermia (with cyanogenic glycosides), tremors, convulsions, stupor, paralysis, coma, and death. Retinal veins and arteries may appear similarly red in color because cyanide blocks cellular utilization of oxygen, elevating venous pO_2.

Respiratory symptoms initially include tachypnea and dyspnea, progressing rapidly to respiratory depression, with hypoventilation and apnea. Noncardiogenic pulmonary edema may be noted after cyanide inhalation or ingestion. Because of increased venous pO_2 and percent O_2 saturation, cyanosis may be absent despite respiratory depression. Severe metabolic acidosis results from anaerobic metabolism with increased lactic acid production.

Cardiovascular signs include initial transient hypertension with reflex bradycardia and sinus dysrhythmia, followed by tachycardia with hypotension and cardiovascular collapse. Electrocardiogram changes include an elevated or depressed ST segment or a shortened ST segment with fusion of the T wave into the QRS complex. Varying degrees of atrioventricular block, erratic supraventricular rhythms, ventricular fibrillation, and asystole may also be seen.

Sequelae of severe acute exposure may include neuropsychiatric manifestations similar to those seen with posthypoxic or post-carbon monoxide encephalopathy, Parkinson-like syndromes, and cardiovascular signs of delayed posthypoxic myocardial lesions.

In smoke-inhalation victims, the hypoxia resulting from carbon monoxide is initially indistinguishable from that due to cyanide, which makes diagnosis of concomitant cyanide poisoning difficult. Characteristics of patients with significant cyanide poisoning secondary to smoke inhalation may include the following:

Persistent hypotension
Coma
Seizures
Cardiac dysrhythmias
Cardiac ischemia

Respiratory depression/apnea
Noncardiogenic pulmonary edema
Peak carboxyhemoglobin levels (>30%)
Persistent metabolic acidosis (pH <7.25)
Increased venous % O_2 saturation and pO_2; absence of cyanosis

Chronic Exposure

☐ **Long-term effects of chronic cyanide exposure include cardiovascular, respiratory, and thyroid function abnormalities.**

Symptoms reported after chronic exposure in occupational settings include breathing difficulty, headache, dizziness, nausea or vomiting, a bitter or almond taste, hoarseness, conjunctivitis, palpitations, chest pains, weight loss, weakness, sleep disturbances, and altered mental status. Mild subclinical abnormalities in vitamin B_{12}, folate, thyroid stimulating hormone (TSH) levels, and thyroid function have been found in silver-reclaiming workers 7 months after cyanide exposure had ceased.

Laboratory Tests

Direct Biologic Indicators

☐ **Whole blood cyanide levels can be used to confirm diagnosis.**

Blood cyanide. Laboratory analysis of whole blood cyanide takes at least 4 to 6 hours, and therapeutic interventions usually must be made before levels are available. However, whole blood cyanide levels are useful in confirming and documenting the diagnosis. One of the most significant problems in measuring cyanide is its instability in collected samples. Consult the laboratory for proper techniques in specimen handling.

Peak whole blood cyanide levels lower than 0.2 micrograms per milliliter (µg/mL) usually do not cause symptoms, although poisoning has occurred at lower levels. Whole blood cyanide levels in smokers may reach 0.4 µg/mL without causing symptoms. At cyanide concentrations between 0.5 and 1.0 µg/mL, untreated patients may be conscious, flushed, and tachycardic. Stupor and agitation can appear with peak blood levels between 1.0 and 2.5 µg/mL. Cyanide levels over 2.5 μg/mL are associated with coma and are potentially fatal without treatment. Typically, plasma cyanide levels are one-tenth the level of the corresponding whole blood specimen but are seldom measured.

Indirect Biologic Indicators

Plasma or serum thiocyanate. Cyanide in the body is biotransformed to thiocyanate. The relative proportion of thiocyanate to cyanide in body fluids is about 1000 to 1. Thiocyanate can be measured in serum or plasma, but interpretation of levels in a cyanide-poisoned patient is difficult. Little correlation has been found between simultaneously obtained whole blood cyanide and plasma thiocyanate levels. Normal plasma thiocyanate can range up to 10 μg/mL in nonsmokers and smokers alike. Lethal thiocyanate levels may range from 50 to 200 μg/mL. The value of thiocyanate levels in the diagnosis of chronic cyanide poisoning is unknown.

☐ **Plasma or serum thiocyanate levels are of limited value in assessing patients with acute cyanide poisoning.**

Other. Whenever smoke inhalation is the potential source of cyanide exposure, carboxyhemoglobin and methemoglobin levels should also be obtained. Both are measured in most hospital laboratories using a co-oximeter, and both may be elevated in smoke-inhalation victims. Either may be measured in heparinized venous blood, although an arterial blood gas specimen is commonly used and provides data on pulmonary function and acid-base status as well.

Pulse oximetry or ear oximetry are unreliable when carboxyhemoglobin or methemoglobin is present and cannot be used to accurately measure oxygen saturation.

Challenge

(6) *In cyanide-poisoned patients, venous pO_2 and percent O_2 saturation may be higher than expected. What is the explanation for this?*

(7) *What are possible causes of the coma experienced by the victims described in the case study?*

(8) *What are the key diagnostic signs of cyanide poisoning in a smoke-inhalation victim?*

(9) *What laboratory tests would help confirm a diagnosis of cyanide toxicity?*

Treatment and Management

Acute Exposure

☐ **Administration of 100% oxygen, followed by antidotes, is the best therapy for cyanide poisoning.**

☐ **Nitrite/thiosulfate is the only approved cyanide antidote in the United States.**

Treatment of cyanide poisoning consists of removal from exposure, administration of 100% oxygen, aggressive cardiorespiratory support, and administration of antidote. Inhalation of amyl nitrite has been recommended as a first-aid measure. Rescuers should not enter areas with potentially high airborne cyanide levels without self-contained breathing apparatus and adequate protective clothing, lest they become secondary victims. If contaminated by liquid or powder, the victim's clothes should be removed and the skin thoroughly cleansed with soap and copious amounts of water. If breathing is absent or labored, ventilatory assistance should be provided. Because of the rapid onset of cyanide toxicity, gut decontamination should follow antidote therapy unless both can be performed simultaneously. Ipecac-induced emesis is contraindicated; activated charcoal should be administered as soon as possible. Gastric lavage is of questionable value unless performed immediately after ingestion. Seizures and hypotension should be treated with anticonvulsants and vasopressors.

Several cyanide-poisoned patients have survived with only aggressive supportive care. Routine use of 100% oxygen is recommended even in the presence of normal pO_2 since oxygen acts synergistically with other antidotes. Metabolic acidosis (pH below 7.35) should be corrected with sodium bicarbonate solution. Close cardiac monitoring is essential; cardiac dysrhythmias often resolve without administration of other pharmacologic agents when the cyanide antidote kit is used. Monitoring for possible development of noncardiogenic pulmonary edema should be instituted.

Hyperbaric oxygen (HBO) is of theoretical benefit because it greatly increases the partial pressure of oxygen in cells. Anecdotal case reports and data from some animal studies support its use in cyanide poisoning. Whether HBO offers any added clinical advantage over 100% normobaric oxygen and the cyanide antidote kit is unknown. Smoke inhalation is frequently associated with chemical pneumonitis, skin burns, carbon monoxide poisoning, and cyanide poisoning; HBO has theoretical or documented benefit in the treatment of all four conditions.

The decision to administer antidotes in acute cyanide poisoning must often be made by clinical suspicion of exposure since pathognomonic signs may be lacking. The odor of cyanide (bitter almonds, "musty") on the victim's breath or in gastric contents is helpful, but its absence does not rule out cyanide poisoning. A hypotensive, bradycardic, acidotic, and acyanotic patient may have cyanide poisoning, especially if CNS, respiratory, and cardiovascular depression subsequently develop. Rapid onset of coma and severe metabolic acidosis together are also indicative of acute cyanide exposure. Cyanide can be measured in body fluids to confirm a diagnosis, but not rapidly enough to guide emergency treatment.

For severely poisoned victims, antidote should be administered as quickly as possible. Only the 3-component Lilly Cyanide Kit is approved in the United States. (Detailed instructions are in the kit.) The kit includes amyl nitrite pearls for inhalation, which can be placed under the victim's nose as a first-aid measure. This step can be bypassed if the IV is already established. The second step is slow IV administration of sodium nitrite with careful blood pressure monitoring, followed within minutes by the third step, IV administration of sodium thiosulfate. Nitrites are believed to induce methemoglobinemia, which detoxifies cyanide by forming cyanomethemoglobin. Thiosulfate serves as a sulfur donor in the rhodanese-catalyzed conversion of cyanide to less toxic thiocyanate.

Methemoglobin levels should be followed serially after the cyanide antidote kit is used. There is no established therapeutic methemoglobin level in the treatment of cyanide poisoning. The determinant of whether further doses of sodium nitrite may be required is the patient's clinical status. Administering further sodium nitrite to a patient who has recovered in order to maintain an arbitrary therapeutic methemoglobin level is both unnecessary and dangerous. One hour after administration of nitrite/thiosulfate, methemoglobin should not exceed 20% (peak level). At methemoglobin levels of 40%, symptoms of cyanosis are evident, and levels of 70% or greater can be fatal, especially in children. If excessive methemoglobinemia occurs, methylene blue treatment can be used. Since this treatment can cause deterioration by re-establishing high cytochrome ferro cyanide levels, it should be administered only by highly trained professionals experienced in managing cyanide poisoning. HBO and exchange transfusion are alternative therapies in severe cases.

Smoke-inhalation victims present a dilemma because administration of nitrite antidote can worsen the effects of carbon monoxide poisoning by forming methemoglobin, which further restricts the oxygen-carrying capacity of the blood. When carboxyhemoglobin levels are greater than 30%, administration of nitrites becomes dangerous. One option is administering the thiosulfate component of the antidote kit first and beginning HBO before giving the nitrite component.

The most promising treatment for smoke-inhalation victims is 100% oxygen and a combination of hydroxocobalamin (vitamin B_{12a}) and sodium thiosulfate, which has been used since the late 1960s in France to treat cyanide-poisoned patients. Hydroxocobalamin does not form methemoglobin nor does it cause hypotension. It is currently an investigational orphan drug undergoing clinical trials in the United States. Rare cases of urticaria reported with use of hydroxocobalamin may have been related to the vehicle in which the material was formerly prepared or to other drugs given concomitantly.

A variety of other agents are effective antidotes for cyanide poisoning, including 4-dimethylaminophenol (DMAP), used clinically in Germany, and dicobalt ethylenediaminetetraacetic acid (cobalt EDTA), used in Britain, France, and Australia. The results of animal studies have shown alpha-ketoglutaric acid, calcium channel blockers, stroma-free methemoglobin solution, and rhodanese to be efficacious. Although several of these cyanide antagonists show clinical promise, none has received FDA approval for routine use.

Chronic Exposure

☐ **The therapy for chronic cyanide poisoning is removal of the patient from the exposure source and treatment of end-organ damage.**

In cases of chronic poisoning, the patient must be separated from the source of cyanide and treated symptomatically. Nutritional deficiencies may exacerbate the chronic effects of cyanide and should be corrected.

Challenge

(10) What treatment should be initiated immediately for smoke-inhalation victims?

(11) After administration of 100% oxygen to the patients described in the case study, the mother responds fully, but the child remains comatose and unresponsive to pain after 40 minutes. What additional action should you take?

(12) What are possible side effects of the cyanide antidote kit?

(13) What are the long-term sequelae in persons acutely or chronically poisoned by cyanide?

Standards and Regulations

A summary of standards and regulations is listed in Table 1.

Table 1. Standards and regulations for cyanide

Agency*	Focus	Level	Comments
ACGIH	Air -Workplace	4.7 ppm	Advisory; TWA[†] for cyanides, based on skin absorption
NIOSH	Air -Workplace	5 mg/m^3	Advisory; 10-minute ceiling limit
OSHA	Air -Workplace	10 ppm	Regulation; PEL[§] for HCN
		5 mg/m^3	Regulation; PEL[§] for cyanide salts
EPA	Air-Environment	N/A	Regulation: to be covered under the Clean Air Act
	Water-Environment	N/A	Regulation; drinking water standard to be proposed in 1990
		3.5 ppb	Advisory; 24-hour coverage to protect aquatic life
	Food	25 ppm	Regulation; residual HCN, when used as a postharvest fumigant in dried beans, peas, and nuts; 250 ppm in spices

[*] ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration

[†] TWA (Time-Weighted Average) = time-weighted average concentration for a normal workday and 40-hour workweek to which nearly all workers may be repeatedly exposed.

[§] PEL (Permissible Exposure Limit) = highest level in air, averaged over an 8-hour workday, to which a worker may be exposed.

Workplace

Air

☐ **The current OSHA permissible exposure limit for HCN is 10 ppm and 5 mg/m³ for cyanide salts.**

The Occupational Safety and Health Administration (OSHA) current permissible exposure limit (PEL) for HCN is 10 ppm and 5 milligrams per cubic meter (mg/m³) for cyanide salts. NIOSH recommends a 10-minute ceiling level of 5 mg/m³ for cyanide salts (4.7 ppm HCN). Air levels of 50 ppm HCN are considered immediately dangerous to life or health.

Environment

Air

☐ **EPA currently has no standard for cyanide emissions to ambient air.**

EPA anticipates cyanide in air will be regulated under the Clean Air Act proposed for 1990.

Drinking Water

☐ **EPA anticipates proposing a drinking water standard for cyanide in June 1990.**

EPA will propose a maximum contaminant level (MCL) for cyanide in drinking water in June 1990. This limit is anticipated to be 200 ppb.

Food

☐ **Foods are regulated when they have been treated with HCN, a postharvest fumigant.**

EPA tolerances for HCN in foods when used as a postharvest fumigant range from 25 ppm in dried beans, peas, and nuts, to 250 ppm in spices. Reference doses were extrapolated from studies of rats fed cyanide salts for 2 years at levels resulting in no observable effect.

Suggested Reading List

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Answers to Pretest and Challenge Questions

Pretest questions are on page 1. Challenge questions begin on page 4.

(1) Many smoke-inhalation victims are poisoned by both carbon monoxide (elevated carboxyhemoglobin levels) and HCN. HCN is formed during pyrolysis of synthetic and natural materials containing nitrogen. The child placed a toy through the heater grill, it ignited, and the fire spread to carpets, drapes, furniture, wire insulation, etc. Under the right conditions, these items could produce HCN, as well as other noxious gases.

(2) The known source of cyanide for the neighbors is contaminated drinking water. Other possible sources include cyanogenic foods; vehicle exhaust, active or passive cigarette smoke, and the fire described in the case study. Information to gather would include other residences, diet, smoking history, occupation, hobbies, and other illnesses.

(3) The two victims would not necessarily have similar blood cyanide levels, even though they were victims of the same fire. The blood cyanide level is a function of the amount and composition of the smoke inhaled. If the mother was in another part of the house and remained unaware of the fire until it had spread, she probably would not have inhaled as much HCN as the child, who was near the fire source. The mother likely received exposure to a lower concentration of smoke and for a shorter duration than the child did.

(4) Causes of an elevated blood cyanide level might include occupational exposure, heavy cigarette smoking, ingestion of large quantities of cyanogenic plants, nitroprusside therapy, smoke inhalation, or a possible laboratory error. The physician should also consider a suicide or homicide attempt using cyanide salts.

(5) Assuming vital signs have been adequately maintained and the patients were well supported, the prognosis is generally good unless significant hypoxia, hypotension, or acidosis occurred before treatment and caused end-organ damage. Survival after 4 hours usually indicates recovery.. A delayed Parkinsonian syndrome can occur after cyanide poisoning, as well as after carbon monoxide poisoning.

(6) The blockage of cellular respiration by cyanide prevents extraction and utilization of the oxygen carried in the arteries. As a result, the presence of unused oxygen will raise the oxygen partial pressure and percent O_2 saturation of the venous blood.

(7) Causes of coma may be grouped as toxicologic or nontoxicologic. Toxicologic causes include carbon monoxide poisoning, cyanide poisoning, or drug overdose. Drug overdose could have resulted in unconsciousness before the fire started. Hypoxemia resulting from any of the above causes may also contribute to continuing coma. Nontoxicologic causes include trauma, particularly to the head, occurring before the fire or to a victim trying to escape the fire.

(8) One of the initial diagnostic signs of cyanide poisoning in a smoke-inhalation victim is the absence of cyanosis despite respiratory depression. The persistence of acidosis and continued bradycardia and hypotension also suggest cyanide poisoning, and antidote should be administered.

(9) A whole blood cyanide level of greater than 1.0 µg/mL is diagnostic of significant cyanide exposure. The laboratory requires 4 to 6 hours to perform this test, however, so it is useful only for confirmation or documentation of the diagnosis and cannot be used to guide emergency management.

An elevated carboxyhemoglobin level (greater than 30%) in a smoke-inhalation victim should provoke suspicion of a concomitant cyanide poisoning. Persistent metabolic acidosis after hypotension has been alleviated, which is consistent with cyanide intoxication, can be determined from the pH or CO_2 content. An valuable clue. However, because respiratory depression or pulmonary damage are likely to occur in such patients, and because inspired oxygen concentrations may vary, a normal venous or mixed venous pO_2 level in a given setting may be unknown.

(10) For smoke-inhalation victims, 100% oxygen should be administered immediately and IV access established.

(11) The biologic half-life of carbon monoxide using 100% oxygen is 60 to 90 minutes. If hypotension, bradycardia, or acidosis persist, cyanide poisoning is likely, and antidote should be administered. Methemoglobin levels should be monitored carefully throughout nitrite therapy. Blood pressure also should be monitored and the nitrite infusion rate slowed if hypotension occurs.

(12) The two major side effects of sodium nitrite from the antidote kit are excessive methemoglobinemia and hypotension. Methemoglobinemia is due to the oxidation of ferrous (+2) iron in hemoglobin to ferric (+3) by nitrite, and, therefore, care must be taken to avoid excessive nitrite doses. Hypotension results from the vasodilating action of nitrite.

(13) Short-term sequelae of patients acutely poisoned by cyanide may include tremors and convulsions. Longer-term effects may include posthypoxic brain damage and myocardial lesions.

The long-term sequelae in persons chronically exposed to cyanide depend on exposure level and duration. In occupational settings, mild abnormalities in vitamin B_{12}, folate, TSH levels, and thyroid function have been reported. Enlarged thyroid, dyspnea on exertion, psychosis, encephalopathy, and myocardial lesions have also been noted but may be due to multiple episodes of subacute poisoning rather than true chronic exposure. In populations consuming large quantities of cassava, endemic goiter, neuropathies, and cretinism have been noted, although dietary deficiencies may have contributed to these effects. Retrobulbar optic neuritis in heavy smokers has also been linked to chronic, low-level cyanide exposure from cigarette smoke.

Whether the neighbors described in the case study who have had chronic cyanide exposure through drinking water will experience long-term effects is difficult to predict. The level of cyanide in their drinking water (212 ppb) is close to what the EPA will propose in 1990 (200 ppb). The amount of cyanide ingested through cassava consumption in the Mozambique population is unknown, and comparisons are not warranted. Persons chronically exposed to low levels of cyanide have not been adequately studied. However, if neurologic, ophthalmologic, and thyroid examinations are normal, reassurance should be given that no ill effects from consumption of the water are evident. The local or state health department could be consulted to obtain assistance with possible control measures to remove cyanide from the well water.

Sources of Information

More information on the adverse effects of cyanide and the treatment and management of cyanide-exposed persons can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Cyanide Toxicity* is one of a series. For other publications in this series, please use the order form on the back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of Director, at (404) 639-6204.

ATSDR June 1990

Case Studies in Environmental Medicine

7

Dioxin Toxicity

Environmental ALERT...

- ☑ *Dioxins bioaccumulate in adipose tissue and can be found in most persons.*
- ☑ *Because dioxins cause cancer in some animals, human exposure is a concern.*
- ☑ *Chloracne is the only overt clinical sign of dioxin exposure in humans.*

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. The Agency for Toxic Substances and Disease Registry (ATSDR) and the Centers for Disease Control (CDC) designate this continuing medical education activity for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association and 0.1 continuing education units for other health professionals. See pages 17 to 19 for further information.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
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Agency for Toxic Substances and Disease Registry

Case Study

A 5-year-old boy with a vesicular facial rash one day after contact with an herbicide

A 5-year-old boy is brought to your office after acute onset of a rash on his face and arms. The rash consists of small blisters with surrounding erythema, which the patient states itch and burn. The boy's mother says she noticed the rash on her son's face last evening, and by morning it had spread to both arms. The child also complains of a headache and stomachache that began early this morning. His temperature is normal.

Further history reveals that the patient and his family moved to this Midwest rural area 2 years ago; their farm is adjacent to a wooded area. Two days ago, workmen from a utility company sprayed beneath the high-voltage power lines that traverse the back edge of the property where the children frequently play during the summer. On questioning, the workmen told the mother they were using an herbicide, but assured her the area would be safe for the children in a few hours. The mother asks you if the defoliant could have contained dioxins, and, if so, whether her child has been affected. Her concern stems from what she has heard about alleged effects of Agent Orange on Vietnam veterans.

Medical history and chart review reveal the child has had no major illnesses. He has had a normal pattern of growth and development, both physical and psychosocial. Immunizations are up to date.

Pretest

(a) What further questions would you ask while taking the medical history?

(b) On what aspect of the boy's physical examination should you focus to address the mother's concern?

(c) What laboratory tests are appropriate to aid in the diagnosis?

(d) Are dioxins likely to be the cause of the boy's rash? Explain.

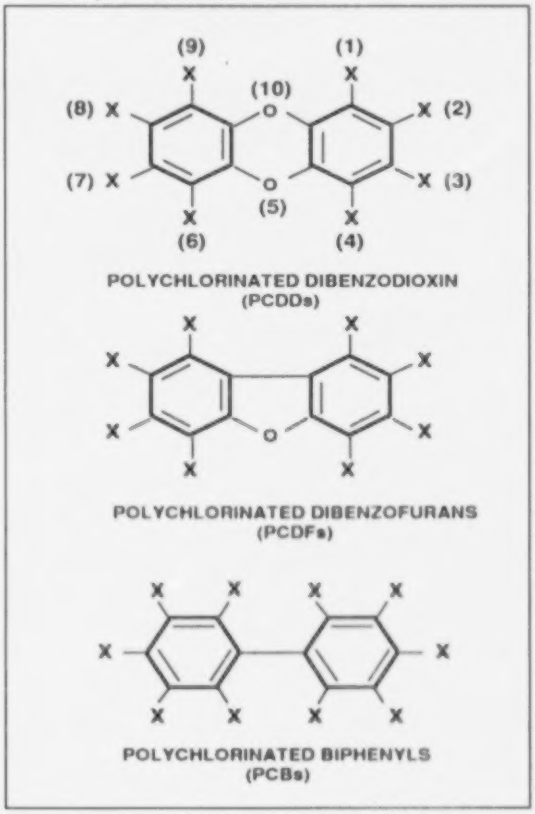
Answers to the Pretest are incorporated in Challenge answers (6) through (10) on page16.

Exposure Pathways

- **The general population's principal route of dioxin exposure is through the food chain.**
- **Other minor dioxin sources are diesel exhaust, chlorine-bleached paper products, and incineration gases.**

Dioxins and furans are terms applied to polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans (Figure 1). They are believed to produce similar health effects and are known to coexist as unwanted contaminants in various materials. Because 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is the most thoroughly studied and most toxic of the 75 dioxin isomers, the term TCDD is used interchangeably with dioxins throughout this monograph. As a pure solid, TCDD is colorless, odorless, lipid-soluble, and only sparingly soluble in water.

Figure 1. Chemical structure of dioxins and related compounds


(9)
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O
POLYCHLORINATED DIBENZODIOXIN
(PCDDs)
POLYCHLORINATED DIBENZOFURANS
(PCDFs)
POLYCHLORINATED BIPHENYLS
(PCBs)

Dioxins, as well as furans, have received much media attention in the past few decades and hence have become a public concern. Dioxins' reputation as extremely toxic is based primarily on tests performed on guinea pigs, the most dioxin-sensitive mammalian species. By comparison, the hamster is 5000 to 10,000 times more resistant in similar toxicity tests. Extrapolation to humans from data based on animal studies is difficult because species vary widely in their sensitivity to dioxins and human risk assessment models are uncertain.

Several human populations exposed to dioxin-contaminated compounds have been studied extensively for health effects. Some Vietnam veterans were potentially exposed to dioxins through the military use of the defoliant Agent Orange (a mixture of 2,4,5-trichlorophenoxyacetic acid [2,4,5-T] and 2,4-dichlorophenoxyacetic acid [2,4-D] contaminated with TCDD). Several areas of the United States have been contaminated as a result of industrial discharges or spraying of dirt roads with dioxin-contaminated waste oils. Three areas that have received notoriety are Love Canal in Niagara Falls, New York; Times Beach, Missouri; and Newark, New Jersey. The most highly publicized accident affecting a residential population was an explosion at a chemical plant that resulted in an airborne discharge of dioxins over Seveso, Italy, in 1976. More than 37,000 people lived in an area that may have been contaminated by dioxins. In all cases, there were no deaths from acute poisoning, and concomitant exposure to other toxic substances may have contributed to the effects that were observed.

Dioxins are formed during the production of many chlorinated organic solvents, hexachlorophene, and the herbicide 2,4,5-T. Emissions from coal-burning power plants, exhaust from diesel engines, and the incomplete burning of wastes containing chlorine, such as PVC plastic form both dioxins and furans; they are also naturally produced in small amounts by volcanoes and forest fires. In nature, dioxins are found adsorbed on air and soil particles. TCDD concentrations in water and on vegetation are generally below present detection limits.

Extremely small quantities of dioxins are found nearly everywhere in the developed world. Minute amounts of TCDD have been detected in paper pulp, formed when chlorine is added during the bleaching process. TCDD reportedly has been leached from milk cartons and from coffee filters (less than 50 parts per trillion [ppt]). The amount of dioxins detected in paper-based personal care products such as disposable diapers, facial or toilet tissue, and paper towels is considered insignificant.

Because dioxins bioaccumulate in the food chain, the major route of human exposure is through food, especially fish, meat, and dairy products. It has been estimated that food accounts for 98% of total adult exposures. TCDD has been detected in fish from Saginaw Bay, contaminated sections of the Great Lakes, and some Michigan rivers, although levels in both the water and fish have decreased over time.

Use of products known or thought to be contaminated by dioxins and furans has been significantly restricted in the last few decades. The U.S. Environmental Protection Agency (EPA) has removed the herbicide 2,4,5-T from the commercial market, and heat-transfer agents using polychlorinated biphenyls (PCBs), which form dioxins during combustion, are being phased out of production and use.

Challenge

(1) Whom would you contact to obtain further information about the herbicide used?

Who's at Risk

- ☐ **Workers in the chemical industry may have increased likelihood of exposure.**
- ☐ **Overt clinical effects from dioxin exposure have been seen primarily after major industrial accidents involving these compounds.**
- ☐ **Fetuses and nursing infants may be at increased risk of dioxin exposure if the mothers have been exposed.**

Dioxins are no longer manufactured in the United States, except for small amounts used for scientific research. Nevertheless, some workers may encounter dioxins as contaminants in certain industrial processes such as the manufacture of chlorinated herbicides, germicides, and organic solvents. Firefighters and cleanup crews involved with capacitor or transformer fires and hazardous waste accidents may also be exposed to dioxins through dermal absorption or inhalation. Municipal and waste incinerator workers may encounter dioxins in smoke, gases, or fly ash formed during combustion processes. Major industrial accidents have been the source of most overt clinical effects from dioxins.

Because TCDD crosses the placenta and accumulates in breast milk, fetuses and nursing infants of contaminated mothers are potentially at increased risk of exposure. Ingestion of contaminated soil due to pica or normal hand-to-mouth activities may contribute to a child's dioxin body burden. No cases of dioxin toxicity have been reported by either of these routes.

Challenge

(2) Would you consider the patient described in the case study at increased risk from dioxin exposure? Explain.

Biologic Fate

Dioxins enter the body by ingestion, inhalation, and dermal absorption. In humans, the following percentages of total absorption have been reported for various exposure routes: inhalation, 25% to 29%; ingestion of contaminated soil, 20% to 26%; and ingestion of contaminated fish, 50% to 80%. Skin was found to absorb up to 3% of the dioxin in contaminated soil.

The metabolic pathway of TCDD for humans has not been established. TCDD orally administered to animals is metabolized relatively slowly, but once metabolites are formed, they are rapidly excreted in the urine and bile. Metabolism is primarily by hepatic detoxification, with the major metabolites consisting of hydroxylated or methoxylated TCDD derivatives, which are then excreted as glucuronide and sulfate conjugates. Unabsorbed TCDD is excreted through direct elimination in the feces. Because of the lipophilic nature of milk, nursing females decrease their body burden of TCDD through lactation. Dioxins distribute to organs according to lipid content and readily accumulate in body fat. In the general population, the background level of TCDD in adipose tissue may be as high as 20 ppt.

The half-life of TCDD ranges from several hours (on the surface of plants) to 7.1 years (in human serum and adipose tissue). On the soil's surface, where TCDD undergoes photodegradation when exposed to ultraviolet light, the half-life is 1 to 3 years. Beneath the soil's surface, the half-life of TCDD can be over 10 years.

- **Dioxins and furans accumulate in adipose tissue.**
- **In animals, the major routes of absorbed TCDD elimination are through lactation and excretion of urine and bile.**

Challenge

(3) Assuming the utility company mentioned in the case study sprayed the area with a dioxin-containing herbicide, when will it be safe for the children to return to the area to play?

Physiologic Effects

☐ **Only two effects of dioxin exposure have been confirmed in humans: chloracne and transient mild hepatotoxicity.**

Dioxins are very toxic to some animal species, but the evidence for corresponding toxicity in humans has not been established. No deaths due to systemic dioxin toxicity in humans have been reported. Only two clinical effects have been repeatedly observed in exposed populations: chloracne and transient hepatic effects. Soft-tissue sarcomas, lymphomas, peripheral neuropathy, birth defects, and reproductive effects have been studied but remain unconfirmed. Because human dioxin exposure always involves mixed exposures, the specific effects of dioxin are difficult to ascertain.

In some animals, TCDD is a potent carcinogen and causes reproductive effects and birth defects. TCDD's toxicity also appears in animals as pathologic effects in the liver, peripheral nerves, hematopoietic and reticuloendothelial systems, and skin. Acute toxicity develops after a latent period of 7 to 10 days, after which the animals experience a rapid wasting syndrome not seen in humans.

Dermatologic Effects

☐ **Chloracne is a hallmark of dioxin toxicity in humans and can persist for years after exposure ceases.**

Acneform lesions may appear as early as 1 to 3 weeks after dioxin exposure. The lesions are small, pale yellow cysts, which arise from altered differentiation of acinar sebaceous basal cells into keratinocytes. The lesions primarily involve the face, especially the periorbital, temporal, and malar areas, as well as the upper body. Most cases of chloracne resolve in 1 to 3 years; one case has been reported to persist for as long as 32 years. Although TCDD is one of the most potent acne-producing agents, chloracne can also be caused by chloro- and bromonaphthalenes, polychlorinated and polybrominated biphenyls (PCBs, PBBs), pentachlorophenol, and tetrachlorobenzene.

Chloracne is the only overt effect of dioxin exposure in human populations; however, the absence of this effect does not rule out dioxin exposure. There is no acceptable dose-response model for chloracne in exposed human populations. It may develop weeks or months after exposure and may be dependent upon individual predisposition. It can result from inhalation, ingestion, or dermal contact and may indicate systemic toxicity.

Six workers who developed chloracne and other illnesses after an industrial accident in Germany had an estimated mean TCDD body burden shortly after the accident of 44 micrograms (µg) with a range of 9.7 to 124 µg. Based on this data, researchers believe that a body burden of 9.7 µg as measured in adipose tissue may be the lowest observable adverse effect level for TCDD-related chloracne in humans. Thirty-two years after exposure, these workers still had detectable levels of TCDD in adipose tissue, and one still had chloracne.

In addition to chloracne, other reported dermal effects include hyperpigmentation, hirsutism, increased skin fragility, and vesicular eruptions on exposed areas of the skin. Concomitant exposure to other agents, however, may have contributed to these effects.

Neurologic Effects

Although dioxins have produced neurotoxic results in laboratory animals, data from human studies have been inconsistent and inconclusive. Peripheral nervous system involvement was studied 6 years after the Seveso accident in 152 victims with chloracne. No case of peripheral neuropathy was found; however, subclinical peripheral nerve impairment was reported in 16 victims. A study of railroad workers exposed to TCDD during cleanup of a tank car spill reported that 43 of 45 workers had findings suggestive of peripheral neuropathy 6 years after exposure, but the validity of the study has been questioned and numerous other epidemiologic studies have found no evidence of neurologic impairment due to dioxin exposure.

☐ **Human epidemiologic data are inconsistent regarding TCDD's neurotoxic effects.**

Hepatic Effects

Although hepatotoxicity has been observed in a variety of animal species, there is no evidence that TCDD causes long-term hepatotoxicity in humans. Some studies have shown a transient increase in liver enzymes without clinical disease. A study of Seveso children potentially exposed to TCDD revealed hepatomegaly and slightly

☐ **Persons exposed to dioxin-contaminated agents had transiently elevated liver enzyme levels.**

elevated serum levels of GGTP (GGT) and SGPT (ALT); however, no apparent liver function impairment was found, and the enzyme levels subsequently returned to normal. Studies of liver function in people in the Times Beach, Missouri, incident also suggested subclinical hepatic effects. Epidemiologic studies of TCDD-exposed workers, however, have shown no difference in serum levels of hepatic enzymes compared with those of matched controls.

Reproductive and Developmental Effects

- **Evidence is lacking that TCDD is a reproductive toxicant in humans.**

Studies of Vietnam servicemen possibly exposed to Agent Orange revealed no overall increase of debilitating birth defects in progeny. A study of the Missouri incident encompassing 410 births reported no statistically significant increase in risk ratios for infant, fetal, and perinatal death, low birth weight, or for several subcategories of birth defects. Studies of the Seveso area have also failed to demonstrate increased risk of birth defects due to dioxin exposure.

Numerous reproductive and developmental effects have been noted in animals exposed to dioxins. These effects include spontaneous abortions in the Rhesus monkey and birth defects in a number of other mammalian species.

Carcinogenic Effects

- **TCDD carcinogenicity in animals is well established; however, human epidemiologic data are inconclusive.**
- **EPA and NIOSH consider TCDD alone to be a probable human carcinogen, and a "cancer promoter" in conjunction with certain other chemicals.**

Although evidence for human carcinogenicity is inconclusive, TCDD is irrefutably an animal carcinogen. The exact mechanisms of action are unknown; therefore extrapolation from animal studies to humans is impossible. Before TCDD's potential human carcinogenic capabilities can be determined, long-term epidemiologic studies in humans are necessary and concomitant exposures must be further defined.

Much of the research in humans has focused on TCDD's ability to induce soft-tissue sarcomas. Epidemiologic studies have produced conflicting results. A study of Swedish workers potentially exposed to TCDD-containing phenoxyacetic acid herbicides indicates an association between herbicide exposure soft-tissue sarcomas at various sites, stomach cancers, and lymphomas. This study was criticized for bias recall, and results of similar research in Finland and New Zealand refute the Swedish study. Of the more than 200 workers exposed to dioxin in a plant explosion in Nitro, West Virginia in 1949, 122 developed chloracne. However, no excess deaths due to cancer were found among the workers 30 years after the incident.

EPA and the National Institute of Occupational Safety and Health (NIOSH) consider TCDD to be a "cancer promoter" in conjunction with certain other chemicals. NIOSH classifies TCDD as a "potential occupational carcinogen." EPA considers TCDD to be a probable human carcinogen. The category of "probable human carcinogen" indicates that EPA considers animal evidence of carcinogenicity "sufficient" and human evidence "inadequate."

Immunotoxic Effects

Abundant animal data indicate that immunotoxicity may be one of the most sensitive toxicologic outcomes for TCDD. Investigations of this endpoint in humans are limited; thus, the importance of TCDD-induced immunotoxicity in humans cannot be evaluated and assessing this endpoint in patients has no clinical value.

☐ **Assessment of immunologic effects in TCDD-exposed patients has no clinical value.**

Challenge

(4) If the child described in the case study had been exposed to dioxin, what health effects might he experience?

(5) What is the child's risk of developing cancer from the exposure described in the case study?

Clinical Evaluation

History and Physical Examination

☐ **A detailed history and physical examination are needed to discover all possible sources of exposure.**

Because dioxins are extremely persistent and bioaccumulate in the food chain, a patient's entire exposure history must be taken into account. If exposure to dioxins is suspected, the history should include the following:

past and present occupational duties
military service in Vietnam involving handling or spraying of herbicides
proximity of residence or work to waste sites or incinerators
contact with herbicides, fungicides, and germicides
dietary composition and habits
history of breast-feeding

In the physical examination, the clinician should review all systems, with particular attention to the skin, liver, and peripheral nervous system. Discovery of a person with dioxin toxicity should suggest that others, such as coworkers, friends, or family members, may have been exposed similarly.

Signs and Symptoms

☐ **Chloracne and elevated liver enzymes may be noted in persons with dioxin toxicity.**

The onset of symptoms after acute exposure to TCDD-containing substances can take days to weeks. Symptoms reported by hazardous waste cleanup crews who later developed chloracne were skin, eye, and respiratory tract irritation; headache; dizziness; and nausea. Other reported symptoms of exposure to TCDD-contaminated compounds include loss of appetite, weight loss, loss of libido, sensory changes, severe fatigue, pain in the abdomen and extremities, memory impairment, uncharacteristic bouts of anger, and insomnia. Many of these signs and symptoms are nonspecific and commonly observed with exposure to other chemicals. Since exposure to TCDD always involves mixed exposures, it is impossible to state with certainty that dioxins caused these effects.

Laboratory Tests

Direct Biologic Indicators

☐ **Blood and adipose tissue tests for TCDD levels are not recommended unless the exposure is massive.**

Adipose tissue and blood serum analyzed for the presence of TCDD by gas chromatography-mass spectrometry (GC-MS), can be quantified to100 parts per quadrillion. Some researchers believe that serum levels correlate with adipose tissue levels in persons with long-term exposure. However, analyses of serum or fat TCDD levels by GC-MS are expensive and time-consuming; therefore, unless exposure has been massive, they are not recommended. Levels of 20 ppt in adipose tissue have been measured in persons with no known exposure to TCDD. In 50 persons exposed in the Missouri incident, the mean ratio of the TCDD level in adipose tissue to that in serum was 1.09 after adjusting both samples for lipid content. Some of the exposed people in the Seveso, Italy, accident had TCDD levels a thousand times greater than the average found in the general unexposed population and did not experience illness.

Indirect Biologic Indicators

Chloracne may be an indicator of dioxin toxicity, although its absence does not necessarily rule out exposure. New cases should be reported to local or state public health authorities. In the absence of chloracne, liver function tests may be the most sensitive indicator of dioxin exposure. This measure, however, is nonspecific, and normal results do not rule out significant exposure or elevated body burden.

❑ **Cases of chloracne should be reported to public health authorities.**

Challenge

(6) What issues should you address in obtaining the medical history of the child described in the case study?

(7) What would be the focus of the physical examination if dioxin exposure were a possibility?

(8) What laboratory tests, if any, would you use to evaluate this child?

(9) What symptoms might develop after exposure to a dioxin-contaminated compound?

Treatment and Management

☐ **No antidote for dioxin toxicity is known; symptomatic and supportive care is the only therapy.**

Treatment of chronic exposure to dioxin-containing agents is primarily supportive, and depends on the agent involved and the presenting signs and symptoms. It is most important to remove the patient from the source of exposure. Chloracne is often refractory and unresponsive to common acne treatments. Long-term topical treatment with dilute retinoic acid and administration of tetracycline to treat secondary pustular follicles have been used. In severe cases, acne surgery or dermabrasion may be effective.

Challenge

(10) What is likely to be the cause of the child's rash and other symptoms mentioned in the case study? What treatment will you recommend?

Standards and Regulations

Before 1965, it was not uncommon for TCDD to be present as a product contaminant in herbicides at concentrations exceeding 30 mg/kg (30 ppm). Today, however, the concentration of TCDD as a product contaminant is limited to 0.01 to 0.05 ppm.

Workplace

Air

☐ **OSHA has not set a workplace standard for dioxins.**

No permissible exposure limit (PEL) has been set for dioxin by the Occupational Safety and Health Administration (OSHA), which is responsible for workplace standards. NIOSH considers TCDD a "probable" human carcinogen and recommends that workplace exposure be reduced to the lowest feasible level.

Environment

Air

EPA currently has no standard for TCDD or other dioxins in ambient air.

☐ **Dioxins in ambient air are not currently regulated.**

Water

The EPA has set a maximum contaminant level for TCDD in drinking water of 5 x 10^{-8} mg/L, or 0.05 ppt. A maximum contaminant level goal of zero will be proposed by EPA in June 1990.

☐ **The legal level for TCDD in drinking water is 0.05 ppt.**

Food

Fish is the greatest potential food source of dioxin contamination. Dioxins readily adsorb to aquatic sediment, and can be ingested by bottom-feeding organisms that are subsequently ingested by predatory fish, thereby bioconcentrating these substances. The U.S. Food and Drug Administration's (FDA) limit for dioxins in fish is 25 ppt TCDD. Since livestock are herbivores, the dioxin bioconcentration potential in these mammals is minimal unless they are grazing on contaminated pasture. There are no standards for meats or other foodstuffs.

☐ **Fish is the only food regulated for dioxin content.**

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Suggested Reading List

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Answers to Pretest and Challenge Questions

Pretest is found on page 1. Challenge questions begin on page 4.

(1) A call to the medical director or the health and safety department of the utility company should provide the answer to the type of herbicide used and its contents. Dioxin-containing herbicides are not likely to have been used in this case since they are no longer being manufactured in the United States.

(2) The patient could be at increased risk of dioxin exposure because he is living in an area of possible soil contamination. Normal hand-to-mouth activity of children can result in ingestion of contaminated soil. Because of the child's age, it is unlikely that he has pica (the abnormal ingestion of nonfood items, commonly found in children aged 2 to 6 years), which could significantly increase the boy's soil intake. Children consume large quantities of milk, which can be a source of dioxins if it comes from cows grazing on contaminated vegetation. The small amount of dioxin leached from paper milk cartons is negligible.

If the family raises its own foodstuffs and if the previous owner of the farm used contaminated herbicides that still may be present in the soil, the current root crops could contain small amounts of dioxins. (Evidence for translocation of dioxins is sparse and inconclusive.) Even though production of herbicides such as 2,4,5–T were discontinued in the United States in 1976, the half-life of dioxin in soil may be 10 years or more, depending on the type of soil. However, this source is likely to be insignificant in terms of health risk.

(3) Even if the herbicide did contain dioxins, these compounds photodegrade rapidly, resulting in a half-life on vegetation of several hours and several days in air. The half-life of dioxins in surface soil is 1 to 3 years, while dioxins beneath the soil surface could have a half-life of 10 years or more. However, dermal absorption from TCDD-contaminated soil is less than 5%. If the children do not ingest the soil, the danger is minimal.

(4) The primary human health effects of dioxin exposure are chloracne, and secondarily, hepatomegaly, elevated liver enzyme levels, and possibly peripheral neuropathy (subclinical changes in nerve conduction velocity).

(5) Although dioxins are proven carcinogens in some animals, their carcinogenic effect in humans requires further study. Even if the herbicide contained TCDD, the risk of cancer for this patient is likely to be insignificant from a one-time exposure that caused no acute effects.

(6) Some of the issues you might address in obtaining the medical history are the following: the type and extent of farming carried on by the family; their lifestyle before coming to this farm; dietary habits, including present or past pica in the child.

(7) During the physical examination, the skin should be carefully examined for evidence of rash, particularly chloracne. Chloracne is a papular, sometimes pustular, lesion located principally on the upper facial areas. The onset of chloracne is not acute, as was the rash described in the case study. In addition, an examination of the abdomen should be conducted, looking for hepatomegaly or hepatic tenderness. A neurologic examination might also be undertaken, with a mental status examination to assess more subtle CNS effects.

(8) Analytical tests for TCDD (adipose tissue, serum) are very specialized and expensive, and generally are not recommended in clinical practice, especially since interpretation in individual cases is difficult. Dioxins may be associated with hepatotoxicity, and liver function tests would be appropriate if there has been known exposure to dioxin.

(9) Symptoms associated with acute exposure to dioxin-containing substances include skin and mucous membrane irritation, headache, fatigue, abdominal pain, memory and personality changes, and insomnia. However, such symptoms are nonspecific and may have other etiologies.

(10) The cause of the child's rash is more likely to be poison ivy, which is common in the wooded areas of the Midwest, an allergy, or exposure to some chemical other than a dioxin. This conclusion is suggested by the acute onset of the rash, its appearance, and its burning nature. Referral to a dermatologist may be warranted if standard measures of treating the rash are not efficacious. The child's symptoms of headache and stomachache may be a result of such factors as stress, food intolerance, or viral infection. If symptoms do not resolve within a day or two, further investigation may be warranted.

ATSDR
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Case Studies in Environmental Medicine

30

Ethylene/Propylene Glycol Toxicity

Environmental ALERT . . .

☑ *Ethylene glycol ingestion results initially in CNS effects. After a characteristic latent period, signs of inebriation may be followed by serious illness, and even death, caused by toxic metabolites.*

☑ *Propylene glycol, which is much less toxic than ethylene glycol, is metabolized to compounds that are normal constituents of the citric acid cycle.*

☑ *No health effects have been reported in persons chronically exposed to levels of ethylene or propylene glycol found in the environment.*

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. See page 23 for more information about continuing medical education credits and continuing education units.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

Disorientation, ataxia, and abdominal symptoms in visitors to a municipal airport

A 67-year-old man is brought to the Emergency Department (ED) of a small community hospital where you are the family physician on call. The patient is experiencing ataxia, dizziness, and vomiting. He is hyperventilating. On physical examination, the patient appears well nourished, agitated, and disoriented. There is no odor of ethanol on his breath. His vital signs include blood pressure, 120/80 mm Hg; temperature, 98.5°F; pulse, 80 beats/minute; and respirations, 40 breaths/minute. Neurologic examination is normal, and there is no nystagmus. Abdominal and cardiorespiratory examinations are also normal.

The patient was brought to the ED by his friend, who relates that the patient said he felt dizzy and began vomiting late last night. This morning he was hyperventilating and continued to vomit. Both men are retired pilots who teach at the ground school at the local airport. Because two other people had collapsed at the airport that morning and were taken by ambulance to another hospital, the friend wonders if the food at the airport cafeteria is responsible. Both he and the patient had hot dogs and coleslaw; yet the friend states that he feels fine.

Although the friend insists that the patient drank only water all day, you order a blood ethanol level, as well as a drug screen, arterial blood gases (ABG), serum electrolytes, BUN, creatinine, and glucose. Blood ethanol and drug screen are negative, and ABG results reveal pH 7.10; $Paco_2$1 20 mm Hg; and Pao_2 95 mm Hg. Other test results are sodium, 145 mEq/L; potassium, 3.8 mEq/L; chloride, 105 mEq/L; bicarbonate, 8 mEq/L; BUN, 20 mg/dL; creatinine, 1.0 mg/dL; and glucose, 80 mg/dL. The calculated anion gap is 32 (normal 12 to 16).

Less than 30 minutes later, a 4-year-old boy is brought to the ED. On examination, you find a sleepy but arousable child. There is no evidence of trauma or focal neurologic signs. Abdominal and cardiorespiratory examinations are normal. Vital signs include rectal temperature, 97.8°F; respirations, 12 breaths/minute; pulse, 78 beats/minute; BP, 94/76 mm Hg. The parents tell you that they were attending a local fliers' club luncheon at the airport. When they found the child staggering and incoherent, they rushed him to the ED; the child vomited in the car. You order the same laboratory tests for the child that you ordered for the 67-year-old patient. From the results of the child's tests, you note that the child is hypoglycemic and slightly acidotic. You calculate an anion gap of 13.

You contact the local health department and are told that they are investigating the earlier incidents at the airport. They suspect that the airport's water supply is contaminated, but they have not identified the contaminant.

Pretest

(a) *What would you include in each patient's problem list? What is the differential diagnosis for an anion gap metabolic acidosis?*

(b) *What additional tests, if any, will you order for these patients?*

(c) *How will you initially treat these patients?*

Answers to the Pretest questions are on page 21.

Glycol Properties

Ethylene glycol and propylene glycol are manufactured chemicals that have similar physical properties and uses. Their chemical structures differ by only one methyl group (ethylene glycol, $HOCH_2CH_2OH$; propylene glycol, $CH_3CH[OH]CH_2OH$). Both chemicals are clear, colorless, odorless, sweet-tasting, highly viscous liquids. They have low vapor pressures at room temperature, indicating low potential for inhalation exposure.

Despite similarities in physical properties and chemical structure, ethylene glycol and propylene glycol have vastly different toxicities. Ethylene glycol is acutely toxic to humans, whereas propylene glycol is a safe additive for foods and medications. Propylene glycol causes poisoning only rarely and under unusual circumstances. These glycols should not be confused with glycol ethers (e.g., ethylene glycol monomethyl ether, also known as methyl cellosolve, and ethylene glycol monoethyl ether), which are suspected reproductive and developmental toxicants. A discussion of ethylene glycol follows; discussion of propylene glycol begins on page 18.

Ethylene Glycol

Exposure Pathways

☐ **Antifreeze, which can contain up to 95% ethylene glycol, is the most common source of ethylene glycol overexposure.**

Ethylene glycol is used in many industries because it has the ability to absorb water and to prevent overheating or freezing. It is used extensively in automotive fluids such as antifreeze, coolants, and hydraulic fluids. Antifreeze, which typically consists of 95% ethylene glycol, accounts for about 65% of the ethylene glycol produced. Ethylene glycol is also used in cosmetics, fat extractants, and as a chemical intermediate. As a solvent, it is found in inks, stains, pesticides, fire extinguishers, foams, polishes, and adhesives. Its heat-regulation properties are employed in air conditioning units and solar energy systems.

Synonyms for ethylene glycol include ethylene alcohol, glycol alcohol, glycol, 1,2-dihydroxyethane, and 1,2-ethanediol. Commercial products containing high concentrations of ethylene glycol include Dowtherm SR1*, Lutrol-9, Norkool, Tescol, and UCAR-17.

Waste streams produced when ethylene glycol is manufactured or used account for the most significant releases of this compound into the environment. In military and commercial aviation, large amounts of ethylene glycol are used for deicing. It is sprayed as an aerosol or mist onto airplane wings to prevent ice buildup. Used in this manner, ethylene glycol can contaminate groundwater near airports through runoff and may expose workers to air levels ranging from <0.05 milligrams per cubic meter (mg/m^3) to 10.4 mg/m^3 (i.e., <0.02 parts per million [ppm] to 4.2 ppm). The Occupational Safety and Health Administration (OSHA) ceiling limit (15-minute sample) for ethylene glycol is 125 mg/m^3 or 50 ppm. Ethylene glycol is also used in coolant loops in spacecraft and in aviator protective clothing; both applications present potential for exposure if leaks occur.

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* Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

☐ **Because of its low vapor pressure and poor skin absorption, ethylene glycol poisonings normally occur by ingestion.**

Ethylene glycol does not persist in ambient air in large amounts because breakdown is rapid (half-life in air is 24 to 50 hours). Its low vapor pressure precludes substantial inhalation exposure at ambient temperatures, and its poor skin absorption prevents significant absorption after dermal contact. Ethylene glycol is miscible with water and adheres to soil (half-life in water and soil is several days). Because it is not fat-soluble, bioconcentration and bioaccumulation are insignificant.

☐ **Ethylene glycol rapidly degrades in the environment.**

Challenge

(1) What questions would health department investigators ask airport visitors and employees to establish the exposure source?

Who's at Risk

Workers in industries that manufacture or use products containing ethylene glycol, particularly operations involving automobile maintenance and aircraft deicing, are at greatest risk of exposure. Although dermal contact is the main route of occupational exposure, vapors or mists can be inhaled when the chemical is heated, agitated, or sprayed.

☐ **Workers in industries producing or using products that contain ethylene glycol are at greatest risk of exposure.**

☐ **The general population has risk of exposure to ethylene glycol primarily through contact with automobile antifreezes and coolants.**

There have been no reports of adverse health effects from chronic environmental exposures to ethylene glycol, and few data exist to evaluate such effects from these exposure scenarios. In the general population, ethylene glycol exposure occurs most commonly through accidental or intentional ingestion of antifreeze. During 1990, 3,242 cases of ethylene glycol exposure were reported to the 72 poison centers participating in the National Data Collection System of the American Association of Poison Control Centers. Of these, 1,451 patients (45%) were examined in health care facilities, 1,147 (35%) became symptomatic, 62 (2%) developed major symptoms, and 5 (0.2%) died. The remainder (577[17.8%]) suffered no ill effects. The general population can also be exposed to ethylene glycol by dermal contact while handling automotive antifreezes, coolants, and brake fluids; however, such exposure is not likely to cause adverse health effects under normal conditions.

Biologic Fate

☐ **Absorption of ethylene glycol by the gastrointestinal tract is rapid; dermal absorption is slow. Inhalation is not an important route of exposure under normal conditions of use.**

Ethylene glycol is rapidly absorbed by the gastrointestinal tract, less rapidly by the lungs, and slowly through the skin. Because of ethylene glycol's low vapor pressure, inhalation is generally not associated with toxicity, although neurologic symptoms including nystagmus and syncope were reported in factory workers chronically exposed to vapor from heated ethylene glycol.

Because it is highly water-soluble, ethylene glycol is evenly distributed throughout the body. It reaches peak tissue levels 1 to 4 hours after ingestion. Approximately 24 hours later, no unchanged ethylene glycol is detected in urine or tissues, indicating rapid biotransformation. The normal serum half-life of ethylene glycol is approximately 2.5 hours.

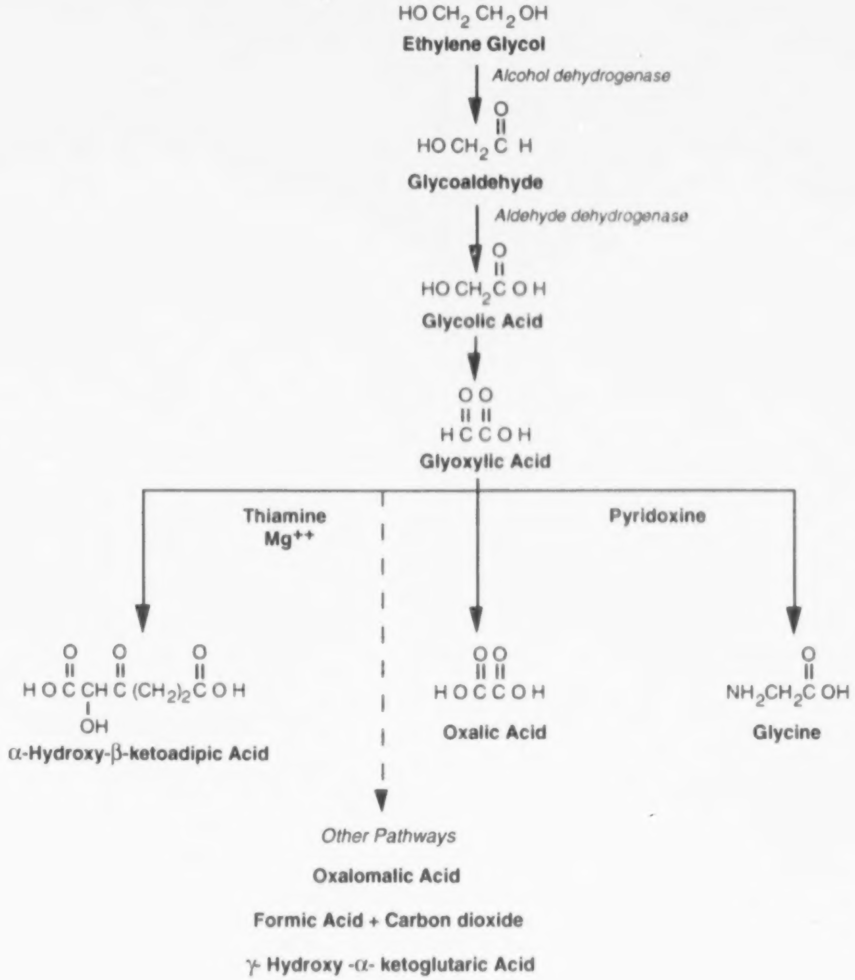
☐ **Ethylene glycol is metabolized in the liver to a variety of more toxic compounds.**

Although ethylene glycol itself has relatively low toxicity, it is metabolized in the liver to a variety of toxic compounds (Figure 1), some of which have elimination half-lives of up to 12 hours. The rate-limiting step in this metabolic process is the conversion of ethylene glycol to glycoaldehyde. Generally, only a small fraction of ethylene glycol (less than 20% in low-dose ingestions) is excreted unchanged in the urine. However, coadministration of ethanol, which inhibits ethylene glycol metabolism by preferentially reacting with alcohol dehydrogenase, can extend the serum half-life of ethylene glycol to 17 hours and increase the percentage of ethylene glycol that is ultimately excreted unchanged. This mechanism is the basis for the antidotal use of ethanol in ethylene glycol-poisoned patients.

☐ **Only a small fraction of absorbed ethylene glycol is normally excreted unchanged in the urine.**

Persons who have impaired liver or kidney function, and children, who have immature hepatic detoxification systems, may be at greater risk of ethylene glycol's initial central nervous system (CNS) effects. However, the clinical courses of illness in such patients may be less severe because of decreased abilities to form toxic metabolites.

Figure 1. Metabolism of ethylene glycol


HO CH2 CH2 OH
Ethylene Glycol
Alcohol dehydrogenase
HO CH2 C H
Glycoaldehyde
Aldehyde dehydrogenase
HO CH2 C O H
Glycolic Acid
H C C O H
Glyoxylic Acid
Thiamine
Mg++
Pyridoxine
H O C CH C (CH2)2 C O H
OH
α-Hydroxy-β-ketoadipic Acid
H O C C O H
Oxalic Acid
NH2CH2C OH
Glycine
Other Pathways
Oxalomalic Acid
Formic Acid + Carbon dioxide
γ- Hydroxy -α- ketoglutaric Acid

Adapted from Hall AH. Ethylene glycol and methanol: poisons with toxic metabolic activation. Emergency Medicine Reports 1992;13 (4):29-38. Used with permission of the publisher.

Challenge

Additional information for the case study: The health department identifies the water contaminant as ethylene glycol. When construction crews at the airport were repairing the water supply system, they inadvertently connected the water from the heating system to the drinking water system. The concentration of ethylene glycol measured at the cafeteria's water source was 9%, or 90,000 ppm. The Environmental Protection Agency (EPA) has a drinking water quality guideline of 7 ppm for ethylene glycol. The lethal dose of 95% ethylene glycol is about 100 mL.

(2) Who in the case study may be at risk of adverse health effects? Explain.

Physiologic Effects

Neurobehavioral Effects

☐ **Unmetabolized ethylene glycol contributes to CNS depression.**

The aldehyde metabolites of ethylene glycol are the cause of many of ethylene glycol's delayed toxic effects. These metabolites inhibit oxidative phosphorylation; cellular respiration; and glucose, protein, and serotonin metabolism. In addition, accumulation of glycolic acid, glyoxylic acid, and, to a lesser extent, oxalic acid, results in metabolic acidosis. (Lactic acid formed during the metabolism of ethylene glycol to oxalic acid also contributes to the metabolic acidosis in patients poisoned by this glycol.)

☐ **Delayed clinical toxicity results from the conversion of ethylene glycol to more toxic metabolites.**

Ethylene glycol poisoning typically has three phases (Table 1). Phase 1, which begins 30 minutes to 12 hours after ingestion, includes signs of inebriation and CNS depression from unmetabolized ethylene glycol and from aldehyde metabolites that peak 6 to 12 hours after ingestion. In some cases, cerebral edema develops. Signs of metabolic acidosis may become apparent late in Phase 1.

Table 1. Clinical course in acute ethylene glycol intoxication

Phase	Onset After Ingestion	Primary Systems Affected	Signs and Symptoms
1	30 minutes to 12 hours	CNS	Ataxia, nystagmus, coma, myoclonus, seizures
		Gastrointestinal	Nausea, vomiting
2	12 to 24 hours	Cardiovascular	Mild hypertension, tachycardia, shock
		Pulmonary	Tachypnea, adult respiratory distress syndrome, pulmonary edema, pneumonitis
		Metabolic	Metabolic acidosis with elevated anion and osmolal gaps, possible tetany from hypocalcemia, and hyperventilation
3	24 to 72 hours	Renal	Flank pain, costovertebral angle tenderness, oliguric renal failure, hyperkalemia

Phase 2, the cardiopulmonary toxicity phase, begins 12 to 24 hours after ingestion. Deposition of calcium oxalate crystals can cause tissue injury in various sites including the meninges of the brain, vascular tree, myocardium, and lung parenchyma. Hypocalcemia may occur secondary to the precipitation of calcium by the oxalate metabolite.

Phase 3, which begins 24 to 72 hours after ingestion, can be manifested by a profound metabolic acidosis. Deposition of calcium oxalate crystals in the kidneys can lead to acute renal failure (irreversible in some cases) and hyperkalemia.

The minimum lethal ingested dose of antifreeze (95% ethylene glycol) for adults is approximately 1.4 mL/kg body weight or about 100 mL of antifreeze for a 70-kg person, although persons who attempted suicide by ingesting 1 to 2 liters of the 95% solution and were treated within 1 hour have survived.

Neurologic Effects

The initial phase of ethylene glycol poisoning is characterized by inebriation caused by unmetabolized ethylene glycol. In acute poisoning, ataxia, slurred speech, and somnolence are common, as are irritation, restlessness, and disorientation. Cerebral edema and crystalline deposits of calcium oxalate in the walls of small blood vessels in the brain may increase CNS depression. In severe poisonings, myoclonic jerks, convulsions, and coma can occur.

☐ **Signs of inebriation are among the first to appear after ethylene glycol ingestion. Any delay in initiating supportive and specific treatment may cause increased severity of adverse effects.**

Several case reports of acute ethylene glycol poisoning have described effects on cranial nerves (e.g., facial paralysis, hearing loss, and bilateral visual disturbances) that occurred 5 or more days after ingestion. These sequelae, however, are not seen often; delay in instituting treatment may contribute to their development.

Respiratory Effects

☐ **Ingestion of ethylene glycol can cause noncardiogenic pulmonary edema.**

Pulmonary effects typically occur 12 to 72 hours after ingestion and may include hyperventilation, respiratory distress syndrome, pneumonitis, and noncardiogenic pulmonary edema. Oxalate crystals in lung parenchyma have been found at autopsy in some ethylene glycol-poisoned patients.

In one study, volunteers who inhaled aerosolized ethylene glycol at a mean concentration of 31 mg/m^3 (12.4 ppm) for 20 to 22 hours per day for 4 weeks experienced throat and upper respiratory-tract irritation. Potential for long-term exposure to ethylene glycol exists in spacecraft if cooling systems leak.

Cardiovascular Effects

☐ **Ethylene glycol ingestion can produce conduction disturbances and cardiac dysrhythmias.**

Cardiovascular effects occur most often in conjunction with respiratory compromise. Deposition of calcium oxalate crystals in the vascular tree and in cardiac tissue may cause the mild hypertension or hypotension and dysrhythmias experienced by patients severely poisoned with ethylene glycol.

Metabolic Effects

☐ **Patients who have ethylene glycol poisoning characteristically have an elevated anion gap and osmolal gap.**

If large doses of ethylene glycol are ingested, poisoning is accompanied by metabolic acidosis, with onset occurring within 24 hours after ingestion. This acidosis is caused primarily by the accumulation of glycolic and glyoxylic acids, although oxalic acid and excess lactic acid may be contributing factors. These acidic metabolites release hydrogen ions, which react with bicarbonate, decreasing the pH in serum and other body fluids. An elevated anion gap results. In addition, ethylene glycol is osmotically active, thereby causing an increased measured osmolal gap. (Osmolality is the osmotic concentration, defined as the moles of solute divided by the number of particles into which it dissociates per kilogram of solvent.)

Tetany can sometimes occur due to hypocalcemia. Hypocalcemia results from precipitation of calcium by the oxalate formed during ethylene glycol metabolism.

Renal Effects

Nephrotoxicity manifests about 24 to 72 hours after substantial ingestion of ethylene glycol. It results from precipitation of calcium oxalate crystals in renal tubules and from the direct cytotoxic action of ethylene glycol metabolites (e.g., oxalic and glycolic acids). Interstitial changes in the kidney are accompanied by acute tubular necrosis. In most cases, the renal injury resolves after recovery; however, it can be irreversible.

☐ **Nephrotoxicity is the dominant effect of serious ethylene glycol poisoning.**

Other Effects

Ethylene glycol is only a minor skin irritant, although a few cases of allergic contact dermatitis have been documented. Acute iridocyclitis has been reported after accidental eye contact with the liquid.

☐ **Ethylene glycol is a skin and mucous membrane irritant.**

No studies in experimental animals have linked ethylene glycol to cancer. One epidemiologic study found an elevated odds ratio for renal cancer in workers exposed to ethylene glycol; however, these workers may have been exposed to other chemicals also.

Studies in experimental animals do not indicate that ethylene glycol causes developmental effects. Although studies in humans have not specifically addressed effects on the fetus, adverse reproductive or developmental outcomes in humans have not been reported.

☐ **Data are inadequate to determine whether ethylene glycol is a carcinogen or a reproductive hazard in humans.**

Challenge

(3) *A week after the water contamination incident, a patient comes to your office. He deices airplanes at the airport and was involved in a major spill yesterday when he was drenched with deicing fluid. He knows that deicing agents contain large amounts of ethylene glycol. He immediately showered and changed clothes after the incident, but he is worried about possible adverse health effects; he wonders if cancer could develop. What will you tell him?*

(4) *A pregnant worker at the airport consults you because she drank tea made with the contaminated water. Although she consumed only a small amount of tea and had no ill effects, she is worried that her fetus will be adversely affected. How will you counsel her?*

ATSDR

Clinical Evaluation

History and Physical Examination

☐ **A detailed history is important in diagnosing ethylene glycol poisoning.**

Ethylene glycol ingestion is a medical emergency requiring prompt recognition and aggressive treatment for a good outcome. The clinical picture in ethylene glycol poisoning varies based upon the amount ingested, the time elapsed since ingestion, and the concurrent ingestion of large amounts of ethanol. Making a correct decision regarding treatment requires a reliable history of the time, route, and magnitude of exposure. However, a detailed history can be difficult to obtain because patients often have an altered mental state. If ethylene glycol poisoning is strongly suspected, supportive and specific treatment should be instituted pending confirmatory laboratory results.

☐ **Prompt recognition and early therapeutic intervention are essential to preventing latent effects and potential sequelae of ethylene glycol poisoning.**

Although there is concern about environmental exposures to ethylene glycol, nearly all cases of ethylene glycol poisoning are due to ingestions. A history of alcohol abuse may suggest ingestion of ethylene glycol as an ethanol substitute. A meticulous search in the home for ethylene glycol-containing compounds should be made in all suspected poisonings. If a product label does not list the chemical ingredients, the regional poison control center may be able to assist. Inquiring about similar symptoms in family members, friends, and coworkers may be helpful in identifying a common source of exposure.

The patient's vital signs should be monitored. Although not specific for ethylene glycol intoxication, hypertension, tachycardia, and low-grade fever have been associated with moderate or severe poisoning. A complete neurologic examination should be performed with special attention directed to gait and balance.

Numerous exogenous toxic substances are associated with an elevated anion gap (Table 2). Only four conditions will cause metabolic acidosis and elevate *both* the anion and osmolal gaps—methanol poisoning, ethylene glycol poisoning, alcoholic ketoacidosis, and diabetic coma. However, when large quantities of ethanol are ingested concomitantly with ethylene glycol, enzymatic conversion to toxic metabolites that produce metabolic acidosis will be inhibited. Inhibiting metabolism also increases the amount of unchanged ethylene glycol circulating in the body. Hence, a patient who has concomitantly ingested ethanol could have an elevated osmolal gap without an elevated anion gap early in the clinical course. The presence of metabolic acidosis and *either* an anion or osmolal gap should alert the clinician to the possibility of ethylene glycol poisoning.

Table 2. Common toxic agents associated with an elevated anion gap

Substance	CNS Depression	Metabolic Acidosis	Ketosis	Increased Osmolality	Characteristic Findings
Methanol	+	++	–	+	Blindness, pink edematous optic disk
Ethanol	+	+	+	+	Alcoholic ketoacidosis
Ethylene glycol	+	++	–	+	Renal failure, calcium oxalate and hippurate crystals, noncardiogenic pulmonary edema
Isopropanol	+	–	++	+	Hemorrhagic tracheobronchitis and gastritis
Salicylates	+	+	+	–	Vomiting, tinnitus, hyperthermia

Adapted from Goldfrank LR. Goldfrank's toxicologic emergencies. 4th ed. Norwalk, Connecticut: Appleton and Lange, 1990:483.

Signs and Symptoms

Patients who have ingested ethylene glycol often progress through three clinical phases. These phases represent a continuum, and an individual patient may have any combination of organ or systemic effects (Table 1, page 7). The time course for each phase, as well as the severity of illness, is dependent on the amount of ethylene glycol ingested and whether ethanol was ingested concurrently.

☐ **Patients with ethylene glycol poisoning may initially appear inebriated and may lack severe toxic manifestations.**

CNS signs and symptoms predominate during the first 12 hours, including headache, slurred speech, dizziness, ataxia, myoclonic jerks, convulsions, coma, and death. In mild cases, the patient may appear inebriated but have no ethanol odor on the breath. Abdominal pain with nausea and vomiting is common.

☐ **After a characteristic latent period, metabolites of ethylene glycol can cause potentially life-threatening illness.**

Phase 2 begins 12 to 24 hours after ingestion and is caused by the products of ethylene glycol metabolism. The primary manifestations are cardiopulmonary with tachypnea, tachycardia, dysrhythmias, hypertension or hypotension, respiratory distress syndrome, and pulmonary edema. Profound metabolic acidosis may be present.

Phase 3 occurs 24 to 72 hours after ingestion if the condition is not treated or is treated unsuccessfully. Acute renal dysfunction secondary to acute tubular or cortical necrosis is seen. Renal dysfunction varies from mild elevation in BUN to overt oliguric renal failure. The renal failure usually resolves but may be irreversible in some cases. Myopathy and bone marrow suppression have also been reported.

In some cases, facial paralysis and other cranial-nerve abnormalities may occur several days after ingestion. These neurologic sequelae are usually found when treatment is delayed or inadequate.

Laboratory Tests

☐ **An elevated anion-gap metabolic acidosis and an elevated osmolal gap combined with urinary crystals suggest ethylene glycol poisoning.**

☐ **Measurement of serum ethylene glycol levels can confirm poisoning.**

The abnormal laboratory findings in ethylene glycol poisoning include an elevated anion-gap metabolic acidosis, an increased osmolal gap, elevated serum ethylene glycol level, calcium oxalate or hippurate crystalluria, and sometimes, hypocalcemia. Arterial blood gases, blood glucose, serum electrolytes, and blood ethanol should be measured in all patients with histories of ethylene glycol ingestion or in whom poisoning is suspected. Results of these laboratory tests will confirm the presence and degree of metabolic acidosis and allow calculation of the anion and osmolal gaps (Table 3). A blood ethanol level will establish whether initial CNS symptoms are due to ethanol. The presence of ethanol will also have a substantial impact on metabolism and therapy.

Table 3. Formulas for calculating anion and osmolal gaps

The serum anion gap (AG) is determined from serum electrolytes measured in mEq/L and may be defined by the formula

$$AG = (Na^{+} + K^{+}) - (Cl^{-} + HCO_3^{-})$$

(Normal anion gap: 12 to 16)

The serum osmolal gap (OG) is most commonly approximated by the formula

$$OG = \text{Osmolality}_{(\text{measured})^{*}} - 2Na^{+} + [BUN \div 2.8] + [\text{Glucose} \div 18]$$

(Normal osmolal gap: <10)

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[*] In this formula, Osmolality$_{(\text{measured})}$ is obtained by the freezing-point-depression method and expressed in milliosmoles per liter (mOsm/L); Na+ in mEq/L; BUN and glucose in mg/dL.

The presence of calcium oxalate or hippurate crystals in the urine, together with an elevated anion gap or osmolal gap, strongly suggests ethylene glycol poisoning. Urinary crystals result from the precipitation of calcium by the oxalic acid metabolite of ethylene glycol or from the reaction of the glycine metabolite with benzoic acid, which forms hippuric acid. The crystals can take many forms including dumbbells, envelopes, or most commonly, needles. Absence of urinary crystals, however, does not rule out poisoning. Because some antifreeze products contain fluorescein, the urine may fluoresce under a Wood's lamp.

An elevated serum level of ethylene glycol confirms ethylene glycol poisoning; significant toxicity is associated with levels greater than 50 mg/dL. Communication with the laboratory is critical in poisoning cases because 2,3-butanediol often found in the plasma of alcoholics can be mistakenly identified as ethylene glycol when the analysis is performed by gas chromatography. Furthermore, propylene glycol may interfere with some assays for ethylene glycol.

Challenge

(5) What additional laboratory tests will you order for the man and child described in the case study on page 1?

Treatment and Management

Treatment should not be delayed pending results of ethylene glycol serum levels if the clinical picture is severe or if the history suggests such poisoning. Treatment advice can be obtained from a regional poison control center or medical toxicologist.

☐ **Correction of metabolic acidosis is an important part of treatment in ethylene glycol poisoning.**

Initial management of suspected poisoning includes basic life support with intubation and mechanical ventilation if required. When the ingestion is recent, measures to prevent ethylene glycol absorption should be taken if the patient's level of consciousness permits. Induced emesis or gastric lavage may be useful if ingestion occurred within 1 to 2 hours. Activated charcoal is not likely to be effective because it does not adsorb ethylene glycol well.

❑ **Specific treatments for ethylene glycol poisoning are ethanol therapy and hemodialysis.**

Specific treatment for ethylene glycol poisoning consists of sodium bicarbonate to correct the metabolic acidosis, ethanol to competitively inhibit conversion of ethylene glycol to its more toxic metabolites, and hemodialysis to remove ethylene glycol and glycolic acid. Although this treatment regimen is effective in most cases, renal failure and death can occur if treatment is delayed.

Ethanol is used to saturate the alcohol dehydrogenase enzyme so that ethylene glycol is maintained in an unmetabolized form and excreted unchanged in the urine. Ethanol therapy should be considered when ethylene glycol levels are greater than 20 mg/dL or when ethylene glycol poisoning is strongly suspected. Patients who have a history of concurrent ethanol ingestion, or who are undergoing hemodialysis, require dosage modification (Table 4). Ethanol can cause hypoglycemia, particularly in children; therefore, blood glucose should be monitored closely. The hypoglycemia that develops in adults is often overlooked because the impairment of mental status is attributed to the ethanol.

Table 4. Intravenous administration of ethanol in ethylene glycol and methanol poisoning

Goal of ethanol therapy: Maintain blood ethanol level between 100 and 150 mg/dL

Loading dose	mg/kg	mL of 10% ethanol/kg
	600 to 800	7.6 to 10
Maintenance dose	mg/kg/hr	mL of 10% ethanol/kg/hr
Chronic alcoholic	154	1.95
Social drinker	110	1.39
Nondrinker	66	0.83
During hemodialysis*	mg/kg/hr	mL of 10% ethanol/kg/hr
Chronic alcoholic	304	3.85
Social drinker	256	3.29
Nondrinker	216	2.73

* Assuming no ethanol is added to dialysis bath.

Adapted from Hall AH. Ethylene glycol and methanol: poisons with toxic metabolic activation. Emergency medicine reports 1992;13(4):29-38.

The loading dose and the maintenance dose should be infused over the first hour of therapy. Decrease to only the maintenance dose in the second hour. If the drinking habits of a patient cannot be determined from the history, assume the patient is in the category of "social drinker," then adjust the dose to achieve a blood ethanol level that remains between 100 and 150 mg/dL.

To prepare 1 liter of 10% ethanol in 5% dextrose in distilled water (D_5W) for intravenous infusion, perform *either* of the following steps:

1. Remove 100 mL of fluid from 1 liter of D_5W; replace with 100 mL of absolute ethanol, *or*

2. Remove 50 mL of fluid from 1 liter of commercially available 5% ethanol in D_5W solution; replace with 50 mL of absolute ethanol.

Blood ethanol and serum glucose levels should be monitored at the end of the loading dose and hourly until the maintenance dose is adjusted. Both should then be monitored two to three times daily, but more frequently during dialysis.

Hemodialysis should be considered if serum ethylene glycol levels exceed 50 mg/dL, if severe acid/base or fluid/electrolyte disturbances persist despite decontamination and ethanol therapy, or if renal failure develops. Hemodialysis should be continued until acidosis is controlled and the serum ethylene glycol level is in the 10 to 15 mg/dL range. Ethanol therapy can be discontinued when the serum ethylene glycol level is below this range.

Thiamine and pyridoxine, two water-soluble B complex vitamins that act as metabolic cofactors, are commonly administered to patients who have ethylene glycol toxicity. Pyridoxine is administered intravenously (100 mg or 1 mg/kg daily until intoxication is resolved). If the vitamins are administered before dialysis, the dose should be repeated after dialysis because they are highly water-soluble and are likely to be removed by the procedure. Thiamine is administered intravenously (100 mg or 1 mg/kg daily) until intoxication is resolved. These cofactors help convert ethylene glycol to less toxic metabolites and may decrease the formation of oxalate.

4-Methylpyrazole is a specific inhibitor of the alcohol dehydrogenase enzyme. It has low toxicity and may replace ethanol in the treatment of ethylene glycol poisoning. At present, 4-methylpyrazole is undergoing clinical trials and is available in the United States only for investigational use.

Challenge

Additional information for the case study: It was later determined that during dinner at the cafeteria, the 67-year-old man had consumed several cups of coffee, while his friend, who did not become ill, drank only soda from a can. The serum ethylene glycol level for the 67-year-old patient is 55 mg/dL; the anion gap is 35.

(6) How will you treat the 67-year-old patient?

Additional information for the case study: The child's ethanol level is 85 mg/dL. You repeat the ethanol test, and again the result is high. The parents are incredulous but admit that the child was not supervised closely during the luncheon, where wine and cocktails were served. Potential ethylene glycol exposure sources for the child could not be identified.

(7) How will you treat the child?

Standards and Regulations

Workplace

OSHA has recognized the respiratory irritation potential of ethylene glycol vapors by setting an exposure limit of 50 ppm (125 mg/m^3) as a ceiling (15-minute sample). The American Conference of Governmental Industrial Hygienists (ACGIH) recommends the same occupational exposure limit.

Environment

Water

The U.S. Environmental Protection Agency (EPA) has an advisory of 7 mg/L or 7 ppm ethylene glycol in drinking water.

Food

The Food and Drug Administration (FDA) has approved ethylene glycol as a component of adhesives used in packaging.

State Guidelines

Some states have defined acceptable ambient air concentrations for ethylene glycol ranging from zero for California to the Texas standard of 1.4 ppm (3.9 mg/m^3) for 30 minutes. Arizona has a drinking water quality guideline of 5,500 µg/L (5.5 ppm); Connecticut has a drinking water quality standard of 100 µg/L (0.1 ppm). Vermont has an enforcement standard of 7.0 mg/L (7.0 ppm) for groundwater.

Challenge

Additional information: The community is worried that the deicing fluid spilled at the airport will contaminate the groundwater supply. They call a town meeting and ask you to speak on the health hazards of ethylene glycol and the regulations governing its presence in air and water.

(8) Where can you find more information on ethylene glycol, and what will you tell the community?

Propylene Glycol

Exposure Pathways

☐ **Propylene glycol is used in various foods, cosmetics, and pharmaceutical products.**

FDA classifies propylene glycol as a Generally Recognized as Safe (GRAS) additive. Propylene glycol acts as an emulsifying agent, humectant, surfactant, and solvent in certain medicines, cosmetics, and food products. Concentrations in foods range from <0.001% in eggs and soups to about 15% in some seasonings and flavorings. The largest amounts of propylene glycol are used in the textile industry, where it is an intermediate in polyester fiber production. Synonyms for propylene glycol include 1,2-propanediol, 1,2-dihydroxypropane, methyl glycol, and trimethyl glycol.

The military uses aerosolized propylene glycol as a smoke screen on the battlefield to conceal the movement of troops. Because it can provide dense smoke without flames, it is also a smoke simulator in various types of fire-training materials. Propylene glycol is sometimes used as a deicing agent; however, ethylene glycol is used more often because it costs less. Propylene glycol is an FDA-approved additive for military dietary rations.

In the general population, propylene glycol exposure occurs primarily through ingestion of food and medications and through dermal contact with cosmetics or topical medications. No adverse health effects are likely to occur from normal use of these products.

Who's at Risk

☐ **Propylene glycol toxicity is not expected in normal environmental or occupational exposures.**

Propylene glycol toxicity has been reported only rarely and in unusual circumstances involving medical applications such as intravenous injection or prolonged dermal contact during treatment of burns. (See Physiologic Effects, page 19.)

Biologic Fate

☐ **Propylene glycol is metabolized to compounds that are normal constituents of the citric acid cycle.**

Absorption of propylene glycol from the gastrointestinal tract is rapid, with maximal plasma concentrations in humans occurring within 1 hour after ingestion. Propylene glycol is metabolized in the liver by alcohol dehydrogenase to lactic acid, then to pyruvic acid. Both of these metabolites are normal constituents of the citric acid cycle and are further metabolized to carbon dioxide and water. About 45% of an absorbed propylene glycol dose is excreted by the kidneys unchanged or as the glucuronide conjugate. The elimination half-life of propylene glycol is about 4 hours.

Physiologic Effects

CNS depression is the primary manifestation of acute propylene glycol poisoning. Metabolic conversion of propylene glycol to lactic and pyruvic acids can contribute to metabolic acidosis with an abnormal anion gap. Unchanged propylene glycol circulating in the body causes hyperosmolality.

☐ **Large doses and unusual circumstances are necessary for the development of propylene glycol toxicity.**

Although propylene glycol is nontoxic under normal conditions, it can cause poisoning in rare and unusual circumstances. In one case, an 8-month-old infant with large surface area second- and third-degree burns was treated for many days with topical silver sulfadiazine containing a large amount of propylene glycol. The infant developed acute metabolic acidosis and cardiorespiratory arrest. The dose of propylene glycol was 9,000 mg/kg/day. Serum propylene glycol levels were highest on day 14 (1,059 mg/dL) when the osmolal gap was 75 mOsm/L (normal: <10 mOsm/L).

☐ **Propylene glycol poisoning is marked initially by CNS depression and an elevated osmolal gap, and later by an increased anion gap.**

Propylene glycol is a common diluent for injectable medications and constitutes 40% of the intravenous form of phenytoin. This high concentration is necessary to maintain a stable preparation and to prevent precipitation of phenytoin crystals. In some patients given intravenous phenytoin, propylene glycol was reported to cause hypotension, cardiac conduction disturbances, and cardiac dysrhythmias; fatal cardiac and respiratory arrests have been reported.

☐ **Unlike ethylene glycol, propylene glycol does not produce nephrotoxicity in humans.**

Propylene glycol has not been associated with nephrotoxicity in humans. Unlike ethylene glycol, propylene glycol is not metabolized to oxalic acid with subsequent deposition of calcium oxalate in the kidneys.

Clinical Evaluation, Treatment, and Management

Although the toxicity of propylene glycol is low, if large amounts are absorbed, an elevated osmolal gap may result. Because propylene glycol is metabolized to lactic acid, ingestion of massive doses of propylene glycol can cause severe metabolic acidosis. Coma, seizures, and hypoglycemia rarely develop in patients with propylene glycol intoxication. Cardiac monitoring is needed if other symptoms are present.

☐ **Treatment for propylene glycol poisoning is supportive and involves hemodialysis and correction of metabolic acidosis using sodium bicarbonate therapy.**

Metabolic acidosis caused by ingestion of large amounts of propylene glycol can be corrected with sodium bicarbonate therapy. Hemodialysis is effective in correcting hyperosmolality by removing propylene glycol from the blood. Ethanol therapy, as described for ethylene glycol-poisoned patients, is unnecessary for patients with propylene glycol poisoning.

Standards and Regulations

There are no workplace or environmental standards for propylene glycol. FDA considers an average daily dietary intake of 23 mg/kg of body weight to be safe for persons 2 to 65 years of age.

Suggested Reading List

General

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Treatment

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Cheng JT, Beysolow TD, Kaul G, et al. Clearance of ethylene glycol by kidneys and hemodialysis. J Toxicol Clin Toxicol 1987;25(1&2):95-108.

Malmlund HO, Berg A, Karlman G, et al. Considerations for the treatment of ethylene glycol poisoning based on analysis of two cases. J Toxicol Clin Toxicol 1991;29(2):231-40.

Stokes JB III, Aueron F. Prevention of organ damage in massive ethylene glycol ingestion. JAMA 1980;243:2065-6.

Government Publications

Agency for Toxic Substances and Disease Registry. Technical report for ethylene glycol/propylene glycol [draft]. Atlanta: US Department of Health and Human Services, Public Health Service, 1992.

Sources of Information

More information on the adverse effects of ethylene glycol and propylene glycol and treating cases of exposure to these glycols can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Ethylene/Propylene Glycol Toxicity* is one of a series. To obtain other publications in this series, please use the order form on the inside back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of the Director, at (404) 639-6204.

Answers to Pretest and Challenge Questions

Pretest questions are on page 1. Challenge questions begin on page 3.

Pretest

(a) The man's problem list includes ataxia, vomiting, agitation, disorientation, hyperventilation, and an elevated anion-gap metabolic acidosis. The child's problem list includes somnolence, ataxia, mental status changes, vomiting, hypoglycemia, low body temperature, and an anion-gap metabolic acidosis.

Common toxic agents associated with an elevated anion gap are shown in Table 2 on page 11.

(b) Additional testing of these patients should include urinalysis, complete blood count, serum osmolality measured by the freezing-point-depression technique, ethylene glycol and methanol levels, and liver function tests.

(c) Treatment for the 67-year-old man is found in Challenge answer 6 on page 22. Additional information on the condition of the child is in *Additional Information for Challenge question 7*, page 16. Treatment for the child is discussed in Challenge answer 7 below.

Challenge

(1) The most common sources in epidemic poisonings include contaminated food, beverages, and water supplies. The investigators would inquire about types of food and drink available at the airport. They would take a detailed history of food and beverage intake from the patients and all others at the airport, in an attempt to find a common factor that would include those who were ill and exclude those who did not become ill. By gathering such data from a large number of people and statistically analyzing the data, the exposure source can usually be identified or possibilities restricted.

(2) The lethal dose of antifreeze (95% ethylene glycol) is about 100 mL, although there is wide variation among reported cases. A cup (240 mL) of the contaminated water would contain about 22 mL of ethylene glycol. This dose could cause significant toxicity. Even mild symptoms of ethylene glycol poisoning would be a concern for air traffic controllers and other airport personnel responsible for judgments affecting many lives. All employees and visitors who consumed beverages or food prepared using water at the airport should be examined.

(3) Absorption of ethylene glycol is slow through intact skin. Because the patient showered and changed clothes immediately, it is unlikely that he will experience toxic effects from the spill. In the case of chronic exposure during the deicing process, few particles from a spraying device are likely to be respirable, so inhalation of ethylene glycol would be minimal. Contact during the deicing process would not contribute substantially to toxicity, especially if protective clothing and respiratory protection were used. There is no evidence that ethylene glycol causes cancer in humans.

(4) You can inform the patient that although no studies in humans specifically assess the effects of ethylene glycol on fetal development, no reports in humans suggest adverse outcomes. In addition, studies in experimental animals indicate that ethylene glycol does not cause developmental effects.

(5) See Pretest answer (b) above. No test for methanol is necessary if it is established that the water was contaminated with ethylene glycol.

(6) Several hours have passed since the ingestion, and emesis or gastric lavage will be of little value. Activated charcoal is likely to be ineffective. However, it is important to act promptly to correct the metabolic acidosis and to prevent further conversion of the remaining ethylene glycol to its toxic metabolites. The acidosis can be corrected with sodium bicarbonate therapy. Intravenous administration of ethanol as described on page 14 will inhibit further metabolism of ethylene glycol. At serum ethylene glycol levels of 50 mg/dL or greater, hemodialysis should be instituted to remove ethylene glycol and its metabolites from the blood. Pyroxidine and thiamine should also be administered.

(7) It is possible that the child is intoxicated with only ethanol or with both ethanol and ethylene glycol. If intoxication is due to ethanol alone, careful monitoring of blood glucose and ethanol should be carried out until intoxication resolves. However, you must consider that ethylene glycol poisoning may be a complication. Because ethanol competitively inhibits ethylene glycol metabolism, you may choose to let the ethanol level decrease naturally to 70 mg/dL, then administer ethanol intravenously to maintain that level. The child should be transferred immediately to a pediatric unit where hemodialysis can be instituted if laboratory results indicate that ingestion of ethylene glycol occurred.

(8) Information about health effects and standards and regulations can be obtained from the *Technical Report for Ethylene/Propylene Glycol* available from the Agency for Toxic Substances and Disease Registry (ATSDR). (For the address and telephone number of this agency, see Sources of Information, page 20.) The air and water standards vary with each state. A search of EPA's Hazardous Substance Data Bank may provide information about the criteria for establishing these standards.

MEDICAL MEMORANDA

Formalin Asthma in Hospital Staff

D. J. HENDRICK, D. J. LANE

British Medical Journal, 1975, 1, 607-608

Few cases of airways obstruction attributable to inhaled formaldehyde have been reported, though it has been suggested that the presence of formaldehyde contributes to the aggravation of chest diseases caused by air pollution (Kotin and Falk, 1964). Occupational "formalin asthma" has been described in a worker in a match factory (Vaughan, 1939) and in workers employed in the tanning and rubber industries (Popa *et al.*, 1969). We report here the use of inhalation provocation tests to investigate the relevance of inhaled formalin fumes to airways obstruction in two hospital staff members continually exposed to this substance in the course of their work.

Case 1

This patient was a 41-year-old nursing sister who began working with formalin in a renal dialysis unit in 1969. She developed a persistent dry cough and episodic attacks of wheezing within a few months which were not improved when she stopped smoking. On two occasions wheezing began four to five hours after exposure for five to 20 minutes to spilled undiluted formalin *B.P.C.* (34-38% solution of formaldehyde in water w/w). There were no other obvious provoking factors. In 1973 her wheezing, accompanied by increasing breathlessness and rhinitis, became persistent and her cough became productive. Treatment with antibiotics and bronchodilators brought little relief and in June 1973 she was obliged to take sick leave, during which she slowly recovered. A chest *x*-ray film showed inflammatory changes in the apical segment of the right lower lobe. The haemoglobin was 13·4 g/dl and the W.B.C. was $13·1 \times 10^9$/l (13 100/mm³), of which $2·1 \times 10^9$/l (2100/mm³) were eosinophils. Routine skin prick tests with 12 common allergens proved negative.

Inhalation provocation tests were begun one month later, when she was receiving no medication. She simulated occupational exposure by "painting" formalin on identical cardboard pieces on different mornings within a confined space. A nose clip prevented her recognizing 25% but not 100% formalin. Ventilatory function was monitored by measurement of forced expiratory volume in one second (FEV_1) using a dry spirometer (Vitalograph) or peak expiratory flow (PEF) using a Wright's meter. The results, expressed as % change, are shown in fig. 1. The late asthmatic reaction seen in test 1 persisted for some days and like that of test 3 showed little objective response to inhaled salbutamol. It was inhibited by prior inhalation of betamethasone 17-valerate 200 µg (test 4). There was no febrile response or significant change in W.B.C. or eosinophil count after any of these tests.

After these studies extractor fans were fitted to the dialysis unit, and undiluted formalin was handled more carefully. The nurse avoided unnecessary exposure and, in particular, no longer cleared up spilled undiluted formalin herself. With these measures her symptoms were completely relieved and she needed no medication.

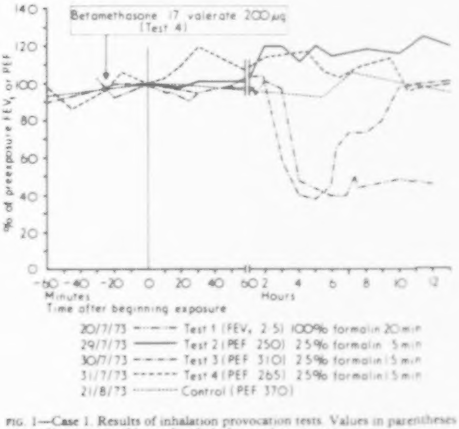

FIG. 1—Case 1. Results of inhalation provocation tests. Values in parentheses are readings obtained immediately before each exposure.

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Case 2

A 59-year-old pathologist had suffered mild asthma as a child and hay fever from the age of 19. Airways obstruction had recurred in 1970 and been slowly progressive ever since. He smoked a pipe and had worked with formalin continually for 17 years. He thought that prolonged exposures worsened his symptoms during the evening after. Routine investigations showed an eosinophilia of $1·19 \times 10^9$/l (1188/mm³), and a skin-prick test produced a positive reaction to grass pollen. There was no other abnormality.

Inhalation provocation tests were conducted as in case 1. Increasing exposures to formalin produced no febrile or haematological response and no significant change in the pattern of ventilatory function from that shown on a control day (fig. 2). The exposure of test 4 was thought to have exceeded the daily maximum encountered naturally in the course of his work. He may consequently be regarded as a control to case 1.

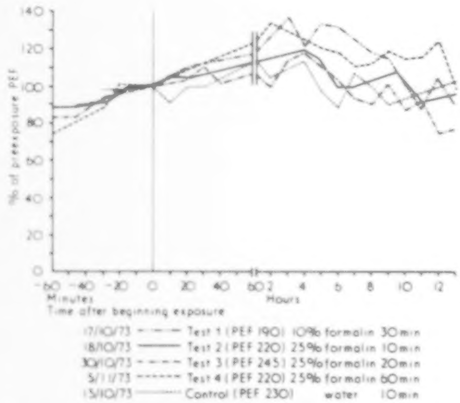

FIG. 2—Case 2. Results of inhalation provocation tests. Values in parentheses are readings obtained immediately before each exposure.

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Comment

The value of inhalation provocation tests as an adjunct to a carefully taken occupational history in the investigation of airways obstruction is well illustrated by these two cases. The suspected aetiological role of formalin was confirmed in one patient but excluded in the other. As a result measures of environmental control were introduced where appropriate, with good effect.

The responses observed in case 1 seemed to be specific asthmatic reactions to formalin fumes. They began between two and four hours after exposure was begun. The greater the exposure the longer the reaction persisted, though the maximum percentage fall in ventilatory function was similar, provided exposure was sufficiently prolonged to provoke a positive response. Similar late asthmatic reactions have been described after the inhalation of fumes of other chemicals, including tolylene di-isocyanate (Pepys *et al.*, 1972) and aminoethyl ethanolamine (Sterling, 1967; Pepys and Pickering, 1972). Such reactions may be inhibited by the prior inhalation of corticosteroid aerosols (Pepys *et al.*, 1974), and this was confirmed in our patient though subsequent treatment did not in the event prove necessary.

We thank the medical illustration department, Radcliffe Infirmary, for the illustrations.

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Pepys, J., and Pickering, C. A. C. (1972). *Clinical Allergy*, 2, 197.
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ENVIRONMENTAL MEDICINE

ATSDR September 1993

Case Studies in Environmental Medicine

31

Gasoline Toxicity

Environmental ALERT . . .

- ☑ ***Leaking underground storage tanks are a growing environmental problem. Of the estimated 1.4 million underground gasoline storage tanks in the United States, about 85% have no protection against corrosion.***
- ☑ ***Gasoline inhalation exposures to the general public during self-service automobile refueling probably are not a significant health risk.***
- ☑ ***Misuse of gasoline as a solvent or cleaner can cause skin and eye irritation and central nervous system toxicity after extensive overexposure.***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. See page 21 for more information about continuing medical education credits and continuing education units.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

A 29-year-old auto mechanic with headaches, irritability, and forgetfulness

A 29-year-old man is brought to your office by his wife. He is reluctant to provide a history but does admit that he has been having frequent headaches for the past month. His wife indicates that at times he is somewhat confused and forgetful. She feels these symptoms have developed since they moved to their new home 6 months ago. She tells you that she has also been irritable and that several of their neighbors have been complaining of a variety of nonspecific symptoms, including headaches and forgetfulness. The wife also says that a nearby gas station was recently fined for having a leaking underground storage tank, and she feels that her family and her neighbors are being poisoned by contaminated drinking water.

The patient's medical history is unremarkable. After completing high school, he entered the Air Force, where he was trained as a mechanic. When he left military service, he and his family moved back to this rural community to be close to his wife's family. He has taken a job at the hardware store as a temporary position and plans to open an automotive repair shop within the next year. He has had an interest in old automobiles since high school. His new position at the hardware store has allowed him to spend an increasing amount of time working on old cars in his garage in back of the house.

The patient's physical examination is unremarkable except for mild dermatitis on the hands, which he attributes to grease and the dirty auto parts he handles. Results of laboratory screening tests, including CBC and liver function tests, are within normal limits.

Pretest

(a) *What further questions would you ask regarding the wife's and neighbors' symptoms?*

(b) *What further questions would you ask regarding the patient's work at the hardware store and his automobile-related hobby?*

(c) *What additional data would be informative regarding the leaking storage tank mentioned by the patient's wife?*

Answers to the Pretest questions are on page 19.

Exposure Pathways

☐ **The principal exposure to gasoline for the general population is through vapor inhalation during automobile refueling.**

Gasoline is a refined petroleum product that is used as a motor fuel. It is highly flammable and potentially explosive. It contains more than 250 hydrocarbons and small quantities of additives and blending agents. The composition of gasoline varies depending on geographic region, season, performance requirements, and blending stocks. The typical hydrocarbon content of liquid gasoline (% volume) is as follows: approximately 60% to 70% alkanes (straight chain, branched chain, and cyclic), 5% to 10% alkenes (straight chain and branched chain), and 25% to 30% aromatics (Figure 1).

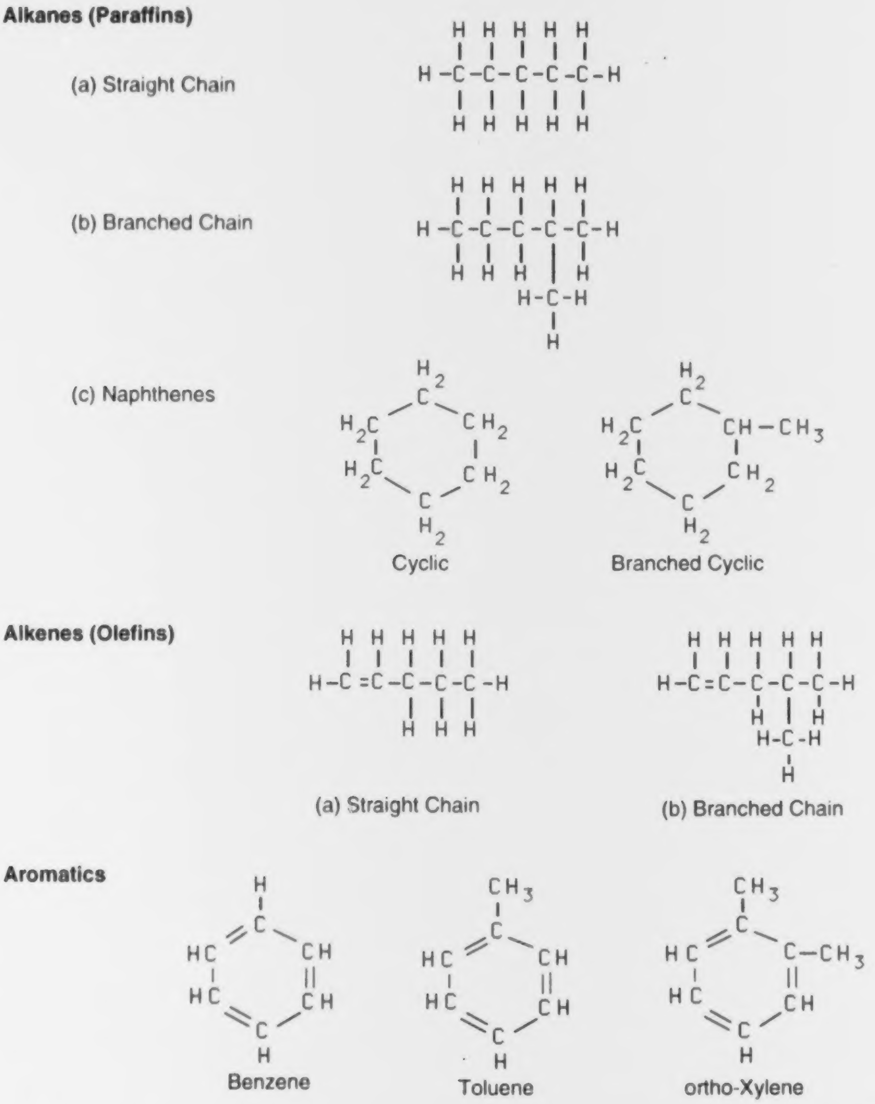
Benzene, a known hematotoxic agent, is present at an average concentration of approximately 1% in U.S. gasoline but can be as high as 5% concentration in European formulations. In addition to hydrocarbons, gasoline contains additives to improve its performance as a motor fuel and to enhance its stability. These additives include antioxidants, metal deactivators, antirust agents, anti-icing agents, detergents, dyes, and antiknock agents (which prevent detonation during combustion in internal-combustion engines and ensure smooth, even burning within the combustion cylinder).

☐ **Gasoline misuse or abuse is a serious exposure concern.**

Gasoline that contains more than 0.05 grams of lead per gram of gasoline is considered leaded gasoline. Organic lead is added to enhance a fuel's octane rating. (The octane rating compares the antiknock properties of a liquid motor fuel to an industry standard; the higher the rating, the more likely the fuel will burn evenly in the combustion chamber.) In 1989, only 10% of the gasoline purchased in the United States was leaded gasoline. Due to the mandated phaseout of leaded gasoline in the United States, this percentage is rapidly decreasing. By 1997, the use of leaded gasoline in this country will have virtually ceased. However, organic lead compounds are still added to gasoline in other parts of the world. The presence of organic lead compounds in gasoline requires the addition of lead-scavenging agents such as ethylene dibromide (EDB). The replacements for organic lead antiknock agents include ethanol, methanol, methyl tertiary butyl ether (MTBE), and tertiary butyl ether (TBE), which are typically added in concentrations of 5% to 15%.

The composition of gasoline vapor differs considerably from the composition of liquid gasoline. In general, vapor pressures of the individual ingredients of liquid gasoline determine the composition of the gasoline vapor. Analysis of the major components in the liquid and vapor phases of a typical blend of the gasoline shows that while the liquid contains about 60% total alkanes, the vapor consists of nearly 90% alkanes (mainly the lighter C_4-C_5 components). Aromatic compounds represent 30% of the liquid phase, compared with only about 2% of the vapor phase. Benzene that is 2.1% of the liquid phase constitutes about 0.9% of the vapor phase. n-Hexane,

Figure 1. Chemical structures for typical members of the three major classes of hydrocarbons in gasoline.


Alkanes (Paraffins)
(a) Straight Chain
(b) Branched Chain
(c) Naphthenes
Cyclic
Branched Cyclic
Alkenes (Olefins)
(a) Straight Chain
(b) Branched Chain
Aromatics
Benzene
Toluene
ortho-Xylene

a neurotoxic agent, is about 2.7% of the liquid phase and 0.9% of the vapor phase. Gasoline additives can also be present in the vapor phase but usually in small amounts.

Exposure to Gasoline Vapor

Gasoline exposure to the general population occurs primarily through inhalation of the vapor during automobile refueling. Of the more than 300 million gallons of gasoline used in the United States annually, the Environmental Protection Agency (EPA) estimates that about 4 million gallons were emitted into the atmosphere as vapor in 1982 alone. About 40% of the vaporization occurred at automotive service stations. Self-service gasoline customers typically experience short-term exposures during refueling of approximately 200 parts per million (ppm) gasoline hydrocarbons and less than 1 ppm benzene for periods of about 2 minutes. The Occupational Safety and Health Administration (OSHA) short-term exposure limit (STEL) averaged over 15 minutes is 500 ppm for gasoline hydrocarbons and 5 ppm for benzene. Thus, the exposure during self-service refueling of automobiles is not likely to be a significant hazard to the public.

Inhalation is the main exposure route for employees of the petroleum and automotive industries. Gasoline vapor is released into the air during refining of crude petroleum, bulk transfer of gasoline, and leaks from storage containers and loading equipment, as well as during refueling of vehicles. Eight-hour time-weighted average measurements for service-station attendants, tank-truck drivers, and refinery workers have shown that potential exposures up to 6 ppm exist for total hydrocarbons and less than 0.1 ppm for benzene. (The occupational permissible exposure limit [PEL] averaged over an 8-hour day is 300 ppm for total gasoline hydrocarbons and 1 ppm for benzene.) Depending on activities, transient exposures for these workers can be much higher.

Exposure to Liquid Gasoline

Human exposure to liquid gasoline occurs by unintentional or intentional ingestion, accidental skin contact, or by misuse of the solvent. Misuse of gasoline, especially to clean and degrease floors, tools, and machine parts, represents the single most important health risk from gasoline for the general public. Gasoline kept in the home for degreasing and to power lawn tools, boats, motorcycles, and recreational vehicles is both a fire and toxic hazard. It should be stored in a properly labeled, tightly sealed, metal container out of the reach of children. Gasoline improperly stored in containers such as soft drink or milk bottles can lead to unintentional ingestion, especially by children. Adults have also unintentionally ingested gasoline while attempting to siphon the fuel.

Contaminated water is a potential source of exposure for the general public, not only through ingestion, but also through inhalation and dermal absorption during bathing and laundering. Gasoline can migrate to groundwater from the soil surrounding a spill or a leaking underground storage tank or pipeline. Leaks from below-ground storage tanks are an increasing environmental problem. Of the estimated 1.4 million underground gasoline storage tanks in the United States, approximately 85% have no protection against corrosion. By one estimate, as many as 100,000 tanks leak millions of gallons of gasoline to groundwater each year; approximately 2,000 leaks are reported each year in New Jersey alone. The state of Maine estimates that leaking underground storage tanks are responsible for the release to groundwater of about 11 million gallons of gasoline each year in that state alone.

Even though chronic ingestion of gasoline through contaminated drinking water is a potential health concern, the federal government has no safety standards for gasoline in water. (EPA has set a maximum contaminant level [MCL] for many of the components of gasoline, but it has no MCL for the mixture.) At three sites near the unintentional release of 1900 metric tons of gasoline into Block Island Sound in Rhode Island, the total levels of C_8 to C_{12} hydrocarbons ranged from 5 to 20 parts per billion (ppb) at a depth of 3.5 meters in the water column. Other unintentional releases to large bodies of surface water have resulted in levels in the range of ppb, but the significance of these levels to human health is not known.

Degradation of gasoline in groundwater and surface waters is expected to be rapid under conditions favorable to microbial activity (i.e., neutral to high pH, moderate temperature, and low salinity). Components such as alkanes, which are not very water soluble, are likely to be degraded by microorganisms, with removal time of days to weeks. Some high molecular-weight components may be ingested by fish and bioconcentrated.

Challenge

(1) What are the potential sources of gasoline exposure for the patient described in the case study?

(2) What steps can be taken to further evaluate the patient's gasoline exposure?

Who's at Risk

☐ **Workers in bulk terminals and on marine tankers, tank-truck drivers, auto mechanics, and service-station attendants have the greatest occupational risk of gasoline exposure.**

The gasoline manufacturing and distribution system involves production of gasoline at oil refineries; transportation via truck, rail, barge, or pipeline to bulk terminals; and further movement from bulk terminals to retail gasoline stations. Refinery workers, persons associated with transportation, gasoline service-station attendants, and workers involved in removal and maintenance of underground storage tanks are at greatest risk of exposure to gasoline. Persons living near gasoline production and distribution systems also have potential exposure. Health risk among consumers and the general public from gasoline-vapor exposure during refueling at self-service gasoline stations is probably negligible.

Persons who misuse gasoline to clean garage floors or use gasoline-soaked rags to clean hands or machinery parts risk toxicity from both inhalation and dermal absorption. Persons who unintentionally ingest gasoline while siphoning and those who intentionally inhale gasoline vapors to obtain euphoric effects risk serious health consequences. The highly flammable and explosive nature of gasoline increases its risk, especially during misuse. Although it is illegal to smoke near a gasoline source, many persons do so, placing themselves and others in great danger. Using gasoline to ignite fires or to increase their rate of burning is also hazardous.

☐ **Persons who misuse gasoline as a recreational drug are at substantial risk for adverse effects.**

Persons who ingest gasoline-contaminated groundwater are at risk of exposure, but the health risks of chronic ingestion of gasoline are unknown. Although numerous cases of leaking underground storage tanks have been documented, contaminated water supplies have rarely contained the individual components of gasoline at concentrations that exceed the EPA maximum contaminant levels.

Persons susceptible to gasoline toxicity include the very young, the very old, pregnant women, and persons suffering from malnutrition.

Biologic Fate

☐ **The most common routes of gasoline exposure are inhalation and dermal absorption.**

The data on the toxicokinetics of gasoline mixtures in humans or animals are sparse. Studies on several of the hydrocarbon components of gasoline are readily available (see *Case Studies in Environmental Medicine: Benzene Toxicity* and *Case Studies in Environmental Medicine: Toluene Toxicity)* and on some additives (see *Case Studies in Environmental Medicine: Methanol Toxicity* and *Case Studies in Environmental Medicine: Lead Toxicity)*. However, the interaction of the components in a gasoline mixture may influence the absorption, distribution, metabolism, and elimination patterns of the individual components.

Gasoline Hydrocarbons

Gasoline can be absorbed by inhalation, ingestion, and dermal exposure routes. In general, the hydrocarbon components with higher blood/gas partition coefficients in the lungs (e.g., xylene, benzene, toluene) have a higher absorption rate during inhalation than components with lower coefficients (e.g., cyclohexane, ethane, ethylene). In time, ingested gasoline is probably absorbed completely because of the high lipophilic properties of the hydrocarbon compounds and the large surface area of the gastrointestinal tract. The rate of dermal absorption is low compared with absorption after ingestion, although the aromatic hydrocarbons, such as benzene, are expected to have higher skin penetration than the alkanes.

☐ **The metabolic pathway for gasoline may be different from the metabolic pathways of individual components of gasoline.**

Data on the biologic fate of gasoline in humans have been obtained primarily through autopsies. In a male who died after unintentional ingestion of gasoline, the highest gasoline concentrations were in the liver, gastric wall, and lungs. Service-station attendants who were exposed to gasoline, most likely by dermal contact as well as inhalation, had elevated blood levels of hydrocarbons such as benzene, toluene, pentane, and hexane.

The metabolism of gasoline mixtures in humans is unknown. However, the interaction of the components will most likely influence the metabolizing enzymes, thereby altering the elimination rate of a component. The increased metabolism of antipyrine in humans and experimental animals exposed to gasoline vapors suggests that mixed-function oxygenase activity is accelerated by gasoline. Some gasoline hydrocarbons are oxidized by liver microsomal-enzyme systems to products that are readily excreted in the urine.

No specific data exist on excretion patterns of gasoline mixtures after exposure. Because alkanes are stable, saturated compounds, they generally are not metabolized. Most of what is systemically absorbed is excreted unchanged through the lungs. Urinary phenol, a biologic indicator of benzene exposure, was found to be elevated in gasoline-pump workers (average 40 milligrams/liter [mg/L]) compared with persons with no occupational exposure to gasoline (less than 20 mg/L).

Gasoline Additives

Tetraethyl lead and tetramethyl lead can be rapidly absorbed through inhalation and skin contact. After absorption, these organic lead compounds are rapidly dealkylated by the liver to trialkyl metabolites that are toxic. The trialkyl metabolites, which are water soluble, can accumulate in the brain; they are slowly metabolized to inorganic lead. Approximately 76% of the lead in these compounds is ultimately excreted as inorganic lead in the urine, 16% in gastrointestinal secretions, and 8% in epithelial structures and sweat.

Methanol is readily absorbed after inhalation or ingestion. A small portion is eliminated unchanged in the breath and urine, but most is metabolized in the liver to formaldehyde, formate, formic acid, carbon dioxide, and water. Formate is the intermediate metabolite believed to be responsible for the delayed effects of methanol poisoning. Recent research shows that formate accumulation in the blood of monkeys parallels the development of ocular disturbances and acidosis. The metabolism of formic acid and formate is dependent, in part, on the vitamin folate. The low level of methanol that could be absorbed during automobile refueling would be metabolized readily to nontoxic compounds through this folate-dependent pathway in most people. (About 10% of the population may be folate-deficient.) However, ingestion of large amounts of gasoline can result in absorption of methanol in a quantity sufficient to quickly overwhelm the folate-dependent metabolic pathway and produce severe toxicity. (See *Case Studies in Environmental Medicine: Methanol Toxicity.*)

Ethanol may be blended into gasoline at concentrations of 5% to 10% as an oxygenate replacement for MTBE. Ethanol is readily absorbed by the gastrointestinal tract and the lungs, whereas absorption through the skin is usually negligible. Approximately 90% of an absorbed ethanol dose is metabolized in the liver to acetaldehyde and acetic acid, and finally to carbon dioxide and water. Ethanol toxicity in humans is rarely attributed to gasoline inhalation exposure.

Depending on the dose and exposure route, 20% to 70% of absorbed MTBE is rapidly exhaled. The remaining MTBE is either metabolized or excreted unchanged in the urine. When metabolized, MTBE is oxidized to formaldehyde and demethylated to tertiary butyl alcohol, which may then be further oxidized to 2-methyl-1,2-propanediol and alpha-hydroxyisobutyric acid. These oxidation products are excreted in the urine.

Physiologic Effects

The major target organ of gasoline exposure is the central nervous system (CNS). Inhalation is the most common route of exposure. Ingestion can result in severe toxicity; single oral doses of approximately 10 milliliters per kilogram (mL/kg) body weight (or about 700 mL for an adult) may be fatal. Much smaller amounts, if aspirated into the lungs, may lead to lipoid pneumonitis.

Contact with liquid gasoline can cause an acute burning sensation in the skin, eyes, and mucous membranes. Prolonged contact with liquid gasoline can defat the skin and cause irritation and dermatitis. Absorption of gasoline probably increases if the skin is broken. Systemic gasoline poisoning due solely to skin exposure has not been documented conclusively.

Central Nervous System Effects

☐ **Prolonged overexposure to high concentrations of gasoline vapor may cause CNS toxicity.**

The major systemic effect of acute gasoline overexposure is CNS depression. Overexposure can lead to facial flushing, ataxia, vertigo, mental confusion, headaches, blurred vision, slurred speech, and difficulty swallowing. At very high concentrations, coma and death can occur within a few minutes without any accompanying respiratory depression or anoxia. In laboratory studies, human volunteers exposed to gasoline vapor developed dizziness and headaches at concentrations greater than 1800 ppm. A 1-hour exposure to 900 ppm caused slight dizziness and irritation of the eyes, nose, and throat. At 10,000 ppm, nose and throat irritation developed within 2 minutes, dizziness within 4 minutes, and signs of intoxication in 4 to 10 minutes. Humans exposed to high, nonlethal concentrations of gasoline usually recover completely, although rare cases of permanent brain damage after massive exposure have been reported.

☐ **Relatively little is known about the potential neurotoxicity of gasoline vapors after prolonged exposures to low concentrations.**

Chronic intentional abuse (e.g., sniffing or "huffing") of gasoline can result in death. The cause of death has been postulated to be either CNS depression, leading to respiratory failure, or a lowering of the myocardial threshold to the dysrhythmogenic effects of circulating catecholamines, leading to fatal dysrhythmia. Chronic abuse of leaded gasoline may cause a range of neurologic effects including encephalopathy, ataxia, and tremor. Among 73 chronic sniffers of leaded gasoline (age range: 4 to 20 years), 69 users (95%) showed definite neurologic effects and had blood lead levels ranging from 30 to 344 micrograms per deciliter (µg/dL). The neurologic effects may have been due to the action of aliphatic and aromatic hydrocarbons, tetraethyl lead, or both.

The potential neurotoxicity associated with repeated low-level exposure to gasoline is undetermined. Appropriate occupational studies are not available and the results of experimental animal studies do not provide a dose-response relationship sufficient to determine a no-observed-adverse-effect level (NOAEL). Subtle neurotoxic effects have been reported in two animal studies. At 8000 ppm, a reduction in overall activity was observed in rats, whereas at the lower concentrations tested (i.e., 4000 ppm and 800 ppm), an increase in physical activity was observed.

Respiratory Effects

☐ **Chemical pneumonitis from aspiration of gastric contents after gasoline ingestion is a concern.**

At high concentrations, gasoline vapor is a respiratory-tract irritant. Pulmonary congestion, edema, acute exudative tracheobronchitis, and intrapulmonary hemorrhage were found when autopsies were performed on persons who died from gasoline overexposure. The lungs of rats chronically exposed to intermediate levels of gasoline vapor showed a progression of lesions characteristic of fibrosing alveolitis (interstitial fibrosis and alveolar collapse). Concurrent with this finding was the observation that surfactant levels in the lung were markedly decreased, suggesting that surfactant deficiency may be involved in the pathogenesis of lung damage due to gasoline inhalation exposure.

Gasoline contains many low-viscosity compounds, which pose a serious pulmonary aspiration hazard. If such compounds are introduced directly into the lung or aspirated during emesis, a severe chemical pneumonitis characterized by pulmonary edema, hemorrhage, and tissue necrosis can result. Pulmonary aspiration of gasoline is a particular concern after ingestion exposure in children, which may occur when gasoline is stored in improperly labeled or inappropriate household containers. Ingestion and pulmonary aspiration may also occur from siphoning gasoline.

Hematopoietic Effects

☐ **Gasoline contains a small percentage of benzene, which is a known hematotoxic agent.**

Several case reports describe hematologic effects in persons with known long-term exposure to gasoline vapor. In these case reports, the blood dyscrasias described (i.e., anemia, hypochromia, thrombocytopenia, and neutropenia) were thought to be due to the benzene in gasoline mixture. Benzene does not pose an identifiable risk to consumers during normal gasoline use because of its low concentration, although it can cause serious damage to the hematopoietic system (see Case *Studies in Environmental Medicine: Benzene Toxicity*).

Carcinogenic Effects

☐ **Lifetime exposure to gasoline vapor causes cancer in experimental animals, but extensive studies do not generally support a similar cancer hazard in humans.**

More than 55 epidemiologic studies of workers exposed occupationally to hydrocarbons have been published. These studies, in general, have not substantiated the carcinogenic effects observed in experimental animals.

A recent case-control study examined kidney cancer deaths reported in refinery workers and concluded there was no association between kidney cancer and exposure to gasoline-like vapors in refineries. Studies of workers in the British and Canadian gasoline distribution systems (from the refinery to the service-station pump) showed instances of excess cases of kidney cancer and leukemia, but these findings were not statistically significant and did not appear related to exposure levels.

☐ **Epidemiologic studies suggest that certain cohorts of refinery workers employed before 1940 may have had an elevated risk of leukemia due to relatively large exposures to benzene.**

A recent study of U.S. gasoline workers in land-based distribution and marine operations found no evidence of increased cancer risk associated with gasoline exposure. A small excess of a subtype of leukemia was seen in the land-based group but was not related to gasoline exposure levels. This observation and the small excess of leukemia cases observed in distribution workers in Britain and

Canada suggest a possible association that needs further evaluation. A meta-analysis in 1989 of several epidemiologic studies did not reveal any clear association between gasoline exposure and leukemia. The authors of the analysis did conclude that some refinery workers, particularly those employed before 1940, may have been at increased risk for developing leukemia caused by the relatively large exposures to benzene that employees experienced in that era.

In 1989, the International Agency for Research on Cancer (IARC) reviewed the world literature on gasoline and concluded that the experimental animal data provide only limited evidence of carcinogenicity and that human epidemiologic studies were inadequate because of lack of complete exposure data, concurrent exposures to other chemicals, and other confounding factors. However, because of the limited evidence from experimental animal studies and the presence of benzene and 1,3-butadiene in gasoline, IARC concluded that gasoline is possibly carcinogenic to humans.

☐ **IARC has classified gasoline as a possible human carcinogen based on the presence of benzene and 1,3-butadiene.**

Reproductive and Developmental Effects

No studies are currently available to evaluate the potential reproductive toxicity of gasoline. Ethanol is the only major gasoline additive with unequivocal evidence of human reproductive or developmental toxicity. Ingestion of as little as one ounce of ethanol daily by pregnant women can cause adverse effects in offspring (e.g., fetal alcohol syndrome). However, gasohol—a blend of gasoline and ethanol—is a very unlikely vehicle for such exposure. A person would have to ingest or inhale large amounts of hydrocarbons to receive sufficient ethanol exposure from gasohol, and the hydrocarbons themselves would cause acute toxicity.

☐ **Several constituents of gasoline can cause reproductive or developmental toxicity in experimental animals but probably do not pose a risk to humans under normal use conditions.**

There is evidence that methanol, toluene, benzene, xylene, 1,3-butadiene, and methyl-t-butyl ether can cause reproductive or developmental effects in experimental animals under various exposure situations. Low-level exposure to those chemicals during normal use and handling of gasoline, however, should not pose human reproductive or developmental health risks.

Challenge

(3) What components of gasoline might explain the patient's symptoms?

(4) What other factors might explain the patient's symptoms and those of his wife and neighbors?

Clinical Evaluation

History and Physical Examination

☐ **The history and physical examination should focus on the CNS.**

When patients have acute symptoms from gasoline overexposure, it is usually apparent where and how the exposure occurred. Persons who are inadequately protected have been overcome by gasoline vapors while cleaning or working in gasoline storage tanks, although this occurrence is rare. Occasionally, emergency spills or leaks can also lead to acute overexposure. Persons who abuse gasoline through intentional inhalation can most often be identified from the history. More problematic are cases in which patients have vague or nonspecific symptoms, and no obvious exposure incident can be elicited.

Specific questions should be asked regarding mouth siphoning of gasoline and use of gasoline as a solvent to clean tools, hands, automobile parts, or garage floors. Open containers of gasoline in a confined space, such as a garage, cannot only pose a serious fire or explosion hazard but can result in potentially toxic vapor concentrations. Because of gasoline's defatting properties, persons who misuse gasoline as a solvent often have dermatitis on their hands.

The physical examination should emphasize the neurologic system because it is the principal target organ for gasoline toxicity. In severe overexposures, life-threatening CNS depression and potential respiratory arrest can occur.

When ingestion of gasoline is suspected, the patient should be evaluated for possible pulmonary aspiration, which may lead to complications of chemical pneumonitis, pulmonary edema, and pulmonary hemorrhage. Ingestion can also cause gastrointestinal disturbances.

Signs and Symptoms

Acute Exposure

Acute gasoline toxicity occurs only rarely today and is most often associated with emergencies involving the cleaning or maintenance of storage tanks, exposures related to large spills or leaks, intentional inhalation of gasoline vapors to obtain euphoric effects, deliberate ingestion in suicide attempts, or unintentional ingestion during siphoning, or misuse of gasoline as a solvent.

☐ **Serious acute exposures are infrequent and usually related to misuse or emergencies involving spills, leaks, or exposures in a confined space.**

The signs and symptoms that develop after acute exposure depend on the route of exposure and the dose absorbed. High-concentration exposures by any route cause CNS depression, which results in confusion, tinnitus, disorientation, headache, drowsiness, weakness, seizures, and coma. Inhalation may produce respiratory-tract irritation, resulting in dyspnea, tachypnea, and rales that may progress rapidly to massive pulmonary edema; a burning sensation in the chest may be present. Ingestion may cause pain and irritation of the mucous membranes, resulting in nausea, vomiting, abdominal pain, and diarrhea. Irritation and dermatitis can occur after skin contact, and conjunctivitis can occur after eye contact.

Chronic abuse of gasoline through sniffing has been reported to cause cardiac dysrhythmias and tachycardia.

Chronic Exposure

Studies have clearly demonstrated that exposures to gasoline and its constituents, including benzene, n-hexane, and 1,3-butadiene during refueling of motor vehicles, are not a serious health hazard for consumers. Organic lead compounds can produce chronic neurologic toxicity, but exposure to such compounds in gasoline is currently negligible in the United States. Potential lead toxicity remains a concern in countries that continue to formulate or use leaded gasoline.

☐ **Repeated exposures to gasoline through refueling of automobiles or ingestion of contaminated water have not been reported to cause chronic health effects.**

Ethanol, methanol, and other additives in gasoline pose potential exposure risks, particularly through unintentional ingestion or suicide attempts. These materials, however, are not hazardous to consumers in the amounts volatilized when gasoline is used as a motor fuel. Hydrocarbon toxicity is likely to occur before toxicity from these additives occurs.

Chronic exposure to gasoline through contaminated drinking water could pose a health risk if concentrations are excessive, especially if the gasoline has a high methanol content; chronic exposure to methanol poses a risk because of its high toxicity after ingestion.

Laboratory Tests

Direct Biologic Indicators

No biologic indicators exist for gasoline that would be of definite value in assessing a person's exposure to gasoline.

Indirect Biologic Indicators

☐ **Appropriate laboratory testing depends on the severity of exposure and existing symptoms.**

Appropriate laboratory evaluation depends on the severity and route of exposure, and on the patient's symptoms. Patients whose symptoms suggest CNS toxicity should have a neurologic evaluation. This evaluation might include neurobehavioral testing and an EEG. After severe, acute overexposure to gasoline, degenerative changes may occur in the liver and kidneys; these effects should be evaluated through routine laboratory testing.

Persons with suspected ingestion should also have a careful pulmonary evaluation, including a baseline chest radiograph to assess possible aspiration. A follow-up chest X ray should be obtained in about 6 hours if pulmonary symptoms develop. Pulse oximetry or arterial blood-gas analyses may be needed to assess oxygenation if significant pulmonary symptoms or cyanosis are present.

Prolonged ingestion of drinking water contaminated with relatively high levels of gasoline may pose a small risk related to benzene exposure. Although no definitive evidence exists to indicate that such exposures are associated with any increased risk of hematologic disorders, in some limited circumstances, periodic hematologic monitoring has been suggested. It is unclear whether such testing can detect early development of leukemia. (See recommendations in *Case Studies in Environmental Medicine: Benzene Toxicity.*)

Challenge

(5) *What further medical workup is indicated for the patient described in the case study?*

Additional information for the case study: Several drinking-water analyses indicate levels of benzene ranging from non-detectable to 0.1 ppb, ethyl benzene from nondetectable to 25 ppb, total xylenes of up to 100 ppb, and toluene up to 10 ppb.

(6) *Is it likely that the patient's complaints and those of his wife and neighbors are from gasoline contamination of the drinking water?*

(7) *Careful history indicates that the patient frequently uses gasoline to clean his hands and to degrease automobile parts. Could this exposure to gasoline account for his complaints?*

Treatment and Management

Acute Exposure

No specific antidotes exist for gasoline; medical management for exposed persons is supportive. After severe inhalation exposure, affected persons should be moved to safety, and resuscitated if necessary. Respiratory compromise may require intubation or surgical creation of an airway.

In cases of ingestion, vomiting should not be induced because of the risk of pulmonary aspiration. Patients should be watched for signs of chemical pneumonitis (coughing and dyspnea) whenever pulmonary aspiration is a possibility. Activated charcoal is of limited use; spontaneous vomiting and diarrhea are likely to occur if a massive dose of gasoline has been ingested.

☐ **Treatment of a patient with acute gasoline exposure is supportive.**

If skin or hair has been in contact with liquid gasoline, remove clothing and flush skin and hair with water (preferably under a shower) for 2 to 3 minutes. Wash with mild soap; rinse thoroughly with water. If eye contact has occurred, the eye should be flushed with water for at least 5 minutes or until pain resolves.

Chronic Exposure

☐ **Avoidance of further exposure is the most important intervention in cases of gasoline misuse.**

The most important intervention in situations where gasoline is misused either to obtain euphoric effects or as a solvent is to ensure that further exposures do not occur. This can usually be accomplished through education and counseling. Persons who intentionally inhale gasoline may require intensive psychological therapy. In most cases, exposure cessation usually leads to complete recovery, even for patients who have evidence of CNS toxicity.

Defatting of the skin and dermatitis that can occur with repeated and prolonged skin contact is managed using skin moisturizers and barrier creams, as well as avoidance of further exposure. For persistent symptoms, a dermatologist should be consulted.

Challenge

(8) What treatment will you recommend for the patient described in the case study?

Standards and Regulations

Workplace

Air

☐ **The current OSHA workplace standard is 300 ppm (8-hr TWA).**

The Occupational Safety and Health Administration (OSHA) mandates permissible limits for occupational exposures. The permissible exposure limit (PEL) for gasoline is 300 ppm as an 8-hour time-weighted average (TWA) and 500 ppm as a short-term exposure limit (STEL). (See Table 1.)

Table 1. Standards and regulations for gasoline

Agency[*]	Focus	Level	Comments
ACGIH	Air—workplace	300 ppm 500 ppm	Advisory; TWA[†] Advisory; STEL[§]
NIOSH	Air—workplace	No criteria	Advisory; as low as possible, based on carcinogenic risk
OSHA	Air—workplace	300 ppm 500 ppm	Regulation; PEL[¶] Regulation; STEL
EPA	Air—environment	No criteria	
	Drinking water		
	Gasoline	No criteria	
	Gasoline components		
	Benzene	0.005 mg/L (5 ppb)	Regulation; MCL[**]
	Toluene	1.0 mg/L (1000 ppb)	Regulation; MCL
	Ethyl benzene	0.7 mg/L (700 ppb)	Regulation; MCL
	Total xylene	10.0 mg/L (10,000 ppb)	Regulation; MCL
	Ethylene dibromide	0.05 µg/L (0.05 ppb)	Regulation; MCL

[*] ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration

[†] TWA (time-weighted average) = concentration averaged over a normal 8-hour workday and 40-hour workweek to which nearly all workers may be repeatedly exposed.

[§] STEL (short-term exposure limit) = concentration to which workers may be exposed on a short-term basis (usually determined by a 15-minute sampling period).

[¶] PEL (permissible exposure limit) = level of contaminant in air, averaged over an 8-hour workday (TWA), to which a worker may be exposed.

[**] MCL (maximum contaminant level) = highest concentration of a contaminant allowed in public drinking water supplies.

Environment

Air

The Clean Air Act Amendments of 1990 mandate that gasoline be reformulated in the nine air quality control regions in the United States with the worst pollution (specifically those that have not attained mandated ozone levels) and provide the option for other areas to adopt these requirements. By 1995, reformulated gasoline will have to meet the following characteristics: 1% maximum benzene content and 15% reduction in total emissions of benzene, 1,3-butadiene, polycyclic organic matter, formaldehyde, and acetaldehyde.

Drinking Water

EPA has not established a maximum contaminant level (MCL) for gasoline in public water systems. EPA has established MCLs, however, for some of the constituents of gasoline. (See Table 1.)

ATSDR

Suggested Reading List

General Reviews

Edminster SC, Bayer MJ. Recreational gasoline sniffing: acute gasoline intoxication and latent organolead poisoning. J Emerg Med 1985;3:365-70.

Harrington JM. Health experience of workers in the petroleum manufacturing and distribution industry: a review of the literature. Am J Ind Med 1987;12:475-97.

Page NP, Mehlman M. Health effects of gasoline refueling vapors and measured exposures at service stations. Toxicol Ind Health 1989;5(5):869-90.

Weaver NK. The petroleum industry. State Art Rev Occup Med 1988:3(3).

Exposure Assessment

Kearney CA, Dunham DB. Gasoline vapor exposures at a high-volume service station. Am Ind Hyg Assoc J 1986;47(8):535-9.

Smith TJ. An exposure assessment for marketing and marine distribution workers in the petroleum industry with potential exposure to gasoline. Washington, DC: Am Petroleum Institute, 1992.

Carcinogenicity

International Agency for Research on Cancer. Occupational exposures in petroleum refining; crude oil and major petroleum fuels. Lyon: IARC 1989:159-201. (IARC monographs on the evaluation of the carcinogenic risks to humans; vol 45.)

Poole C, Satterfield MH. A case-control study of kidney cancer among petroleum refinery workers. Washington, DC: Am Petroleum Institute, 1990.

Wong O, Harris F. A mortality study of marketing and marine distribution workers with potential exposure to gasoline in the petroleum industry. Washington, DC: Am Petroleum Institute, 1992.

Wong O, Raabe GK. Critical review of cancer epidemiology in petroleum industry employees, with a quantitative meta-analysis by cancer site. Am J Ind Med 1989;15:283-310.

Related Governmental Publications

Northeast States for Coordinated Air Use Management, Air Toxics Committee. Evaluation of the health effects from exposure to gasoline and gasoline vapors. Final Report. Boston: NESCAUM 1989.

Environmental Protection Agency. A toxicological assessment of the unleaded gasoline contamination of drinking water. Washington, DC: US Environmental Protection Agency, 1989.

Sources of Information

More information on the adverse effects of gasoline and treating cases of gasoline exposure can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Gasoline Toxicity* is one of a series. To obtain other publications in this series, please use the order form on the inside back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of the Director, at (404) 639-6204.

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Answers to Pretest and Challenge Questions

Pretest questions are on page 1. Challenge questions begin on page 5.

Pretest

(a) Because an environmental exposure is being considered, further information should be obtained about the reported symptoms of the wife and the neighbors.

Detailed questions regarding the woman's irritability would be appropriate. A review of neurologic symptoms is indicated. In addition, the relationship of those symptoms to the family's relocation should be explored. Because there may be other explanations for her complaints, discuss her recent relocation and adjustment to the new community. Are there new stresses in her life that could account for the symptoms? Explore recent onset of any unrelated diseases and possible pregnancy. A detailed description of the nonspecific symptoms of the neighbors should also be elicited from the couple if possible. Until there is further evidence to indicate a potential environmental concern, the neighbors should not be interviewed directly. Follow-up with the neighbors or the health department will be appropriate when a potential public health problem has been established.

(b) The patient's potential occupational exposures at the hardware store should be explored (e.g., filling propane tanks, mixing paints, cleaning recent spills). Do coworkers have any related symptoms?

In addition, working on old cars in a garage can involve exposure to many materials. Detailed information should be obtained regarding the solvents, paints, welding fumes, greases, or other agents that the patient may encounter.

The composition of the materials used or handled, the quantities involved, the duration of exposure, and any protective measures that are used should be considered in making an overall assessment.

(c) Because the safety of the drinking water has been questioned, information should be obtained regarding the water supply to the house. Is the water supplied by a public water system or from a local or household well? If the water is supplied through a public water system, it is highly unlikely that a gasoline storage-tank leak near the patient's house could lead to contaminated water. If the water is obtained through a local well (probable in the case study because they live in a rural community), a potential leak should be investigated. A call to the regional EPA office could provide specific information about the water system and the results of any water analyses.

Challenge

(1) The patient has potential gasoline exposure from the following sources:

- automobile refueling
- consuming contaminated drinking water
- working on old cars

(2) Exposure of the general public to gasoline vapor through automobile refueling is low and does not pose an identifiable health risk to consumers. The patient's exposure to gasoline through contaminated drinking water is possible, although it is unlikely that levels of benzene, toluene, or other constituents would be at a level that could produce toxicity. The lack of eye and respiratory-tract irritation from volatilization of gasoline in the home

water supply during showering, dishwashing, laundering, and other activities does not indicate significant exposure by this route. To evaluate this exposure route, levels of gasoline constituents in the household drinking water should be measured and more information about the storage-tank leak should be obtained.

The potential for gasoline or hydrocarbon-based solvent exposure through the patient's hobby should be explored carefully. Detailed information should be obtained regarding the patient's use of gasoline as a solvent to clean his hands or automobile parts. What is the frequency and duration of exposure? Is gasoline stored in open containers in the garage? Is the garage ventilated while he is working? If there is any indication of recreational gasoline abuse, his symptoms could be related to overexposure.

(3) Several of the hydrocarbons in gasoline can produce CNS toxicity. The most likely components, based on their percentage volume, would be toluene and xylene. n-Hexane can also cause CNS, as well as peripheral nerve, toxicity; however, the low concentration of n-hexane in gasoline makes it an unlikely candidate.

(4) Nonspecific symptoms can be very difficult to evaluate. If there is no objective evidence of disease and no laboratory or physical abnormalities, the clinician should consider other contributory factors. Are the readjustment stresses to the new community? Are there financial or marital difficulties or other external considerations?

(5) If a careful history indicates that the patient has had recent onset of frequent headaches, as well as other neurobehavioral symptoms, a thorough neurologic examination should be performed. If deficits are demonstrated, further neurologic workup, such as scans, EEG, and neurobehavioral testing, is indicated. If gasoline toxicity is a consideration, liver and kidney function should be evaluated, although abnormalities are unlikely unless there has been severe acute overexposure.

(6) No, the measured results are well within normal limits and do not indicate a toxic exposure. Given the potential variability of water analyses, it would be appropriate to confirm these insignificant levels by performing two or three analyses.

(7) Occasional misuse of liquid gasoline to clean hands or machinery parts is unlikely to cause significant toxicity, although the practice may present a serious fire or explosion hazard. Repeated skin contact can lead to defatting of the skin and dermatitis. The dermatitis on the patient's hands in this case study could indeed be from dermal contact with liquid gasoline.

Prolonged and repeated misuse of gasoline as a solvent or cleaning agent can, however, cause significant toxicity. If the patient has frequent extensive skin contact with liquid gasoline or is frequently exposed to high concentrations of gasoline vapors via open containers of gasoline in a confined space, his headaches, confusion, and forgetfulness could be from gasoline overexposure.

(8) The single most important intervention in this case would be to counsel the patient on the hazards of gasoline and to eliminate further misuse. Removal of exposure would most likely lead to a complete resolution of symptoms without further sequelae. In a few cases, some residual deficits might persist.

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HANTAVIRUS PULMONARY SYNDROME: A CLINICAL DESCRIPTION OF 17 PATIENTS WITH A NEWLY RECOGNIZED DISEASE

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Abstract *Background.* In May 1993 an outbreak of severe respiratory illness occurred in the southwestern United States. A previously unknown hantavirus was identified as the cause. In Asia hantaviruses are associated with hemorrhagic fever and renal disease. They have not been known as a cause of human disease in North America.

Methods. We analyzed clinical, laboratory, and autopsy data on the first 17 persons with confirmed infection from this newly recognized strain of hantavirus.

Results. The mean age of the patients was 32.2 years (range, 13 to 64); 61 percent were women, 72 percent were Native American, 22 percent white, and 6 percent Hispanic. The most common prodromal symptoms were fever and myalgia (100 percent), cough or dyspnea (76 percent), gastrointestinal symptoms (76 percent), and headache (71 percent). The most common physical findings were tachypnea (100 percent), tachycardia (94 percent), and hypotension (50 percent). The laboratory findings included leukocytosis (median peak cell count, 26,000 per cubic millimeter), often with myeloid precursors, an increased hematocrit, thrombocytopenia (median lowest platelet count, 64,000 per cubic millimeter), prolonged prothrombin and partial-thromboplastin times, an elevated serum lactate dehydrogenase concentration, decreased serum protein concentrations, and proteinuria. Rapidly progressive acute pulmonary edema developed in 15 of the 17 patients (88 percent), and 13 patients, all of whom had profound hypotension, died (case fatality rate, 76 percent). Increases in the hematocrit and partial-thromboplastin time were predictive of death.

Conclusions. Infection with a newly described hantavirus causes the hantavirus pulmonary syndrome, which is characterized by a brief prodromal illness followed by rapidly progressive, noncardiogenic pulmonary edema. (N Engl J Med 1994;330:949-55.)

On May 14, 1993, the New Mexico Office of the Medical Investigator was notified of the unexplained deaths of a couple living in the same household in rural New Mexico: a 21-year-old woman and a 19-year-old man. Both died of acute respiratory failure — the man within five days after the woman. By May 17, Indian Health Service physicians had reported five deaths from adult respiratory distress syndrome among previously healthy adults. Surveillance was initiated for an influenza-like illness followed by the rapid onset of unexplained respiratory failure. On May 22, the brother of the initial patient had an acute onset of a similar illness, as did his wife five days later; by June 7, 24 cases, including 12 deaths (some identified retrospectively as occurring since March 1993), meeting the clinical case definition had been reported and were under investigation.[1] All the subjects lived in or near the Four Corners area of New Mexico, Arizona, Colorado, and Utah.

Illnesses considered in the initial differential diagnosis included pneumonic plague, leptospirosis, inhalational anthrax, rickettsial infections, pulmonary tularemia, atypical bacterial and viral community-acquired pneumonias, legionellosis, meningococcemia and other sepsis syndromes, and illnesses caused by viruses not commonly seen in the United States (flavivirus, arenavirus, and bunyavirus). There was no evidence of exposure to known toxic agents. Laboratory tests for bacterial and viral pathogens and a variety of toxic agents were negative, and the initial autopsy findings suggested that bacterial or parasitic causes were unlikely. The results of laboratory studies of serum and tissue samples from several patients suggest-

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The opinions expressed in this paper are those of the authors and do not necessarily reflect the views of the Indian Health Service.

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ed an acute infection with a new species of hantavirus. This report describes the first 17 patients with this illness, which was characterized by rapidly progressive respiratory and hemodynamic deterioration due to a strain of hantavirus previously unrecognized in North America.

The hantavirus genus belongs to the Bunyaviridae family and includes the causative agents of a group of febrile nephropathies known collectively as hemorrhagic fever with renal syndrome, which occurs throughout Europe and Asia.[2] The hallmarks of hemorrhagic fever with renal syndrome are hematologic abnormalities, prominent (often severe) renal involvement, and increased vascular permeability.[3] Hantaan virus is the prototype hantavirus; isolated in 1977, it occurs predominantly in the Russian Far East, China, and Korea.[4] Severe disease associated with the Hantaan virus is characterized by five phases: febrile, hypotensive, oliguric, diuretic, and convalescent. However, 30 to 40 percent of patients have minimal illness, and in only 20 to 30 percent is the illness moderate or severe.[5-7] Respiratory symptoms are generally not pronounced, and pulmonary involvement has not been a prominent feature of the known hantaviral syndromes.[8] Several species of rodents in the United States have been shown to be infected with hantaviruses. Although seroprevalence studies have detected antibodies to hantaviruses in a small percentage of people in the United States, there were no reports of acute illness resulting from hantavirus infection acquired in North America before the outbreak of cases described in this report.[9,10]

METHODS

The case definition of acute, unexplained respiratory distress syndrome consisted of either of the following findings in any patient presenting after January 1, 1993: unexplained adult respiratory distress syndrome or radiographic evidence of acute, bilateral, interstitial pulmonary infiltrates with hypoxemia (arterial oxygen saturation, less than 90 percent while the patient is breathing room air), or autopsy findings of unexplained, noncardiogenic pulmonary edema. Physicians in New Mexico, Arizona, Colorado, and Utah were requested to report cases meeting this definition to their state health departments.

Serum samples were tested for antibodies against a panel of heterologous hantaviral antigens, and tissue samples were tested for evidence of hantavirus infection by means of the polymerase chain reaction in frozen lung-tissue specimens or immunohistochemical staining of formalin-fixed specimens[11] (and Centers for Disease Control and Prevention [CDC]: unpublished data). A case of unexplained respiratory distress syndrome was considered to be confirmed as hantavirus infection if the results of antibody, polymerase-chain-reaction, or immunohistochemical testing were positive. Thirty-one patients meeting the case definition were identified by surveillance in the four-state area. As of July 11, 1993, 17 of the 31 had confirmed hantavirus infection; medical records were available for 16 of these patients. One additional patient, whose illness began before the surveillance period (November 1992), was identified and is included in the analysis.

Autopsy examinations were performed in 9 of 13 deceased patients (69 percent) at the New Mexico Office of the Medical Investigator. Autopsies were performed in 12 patients elsewhere, and the histopathological findings reviewed at the CDC. Medical records were abstracted by a single reviewer using a standardized data-collection form. Interviews with physicians were conducted to supplement the medical history in the case of two patients whose medical records were incomplete.

Data were stored and analyzed with the use of Epi-Info, version 5.01 (CDC and World Health Organization, Atlanta). A multiple logistic regression with a stepwise procedure was performed with SAS software (SAS Institute, Cary, N.C.).

RESULTS

During the study period, acute hantavirus infection was confirmed in 18 patients, 14 of whom died (78 percent). The median age was 31.0 years (mean, 32.2; range, 13 to 64); 11 of the patients (61 percent) were women. Thirteen patients (72 percent) were Native American, four (22 percent) were white, and one (6 percent) was Hispanic. Twelve patients (67 percent) resided in New Mexico, five (28 percent) in Arizona, and one (6 percent) in Colorado. In 12 patients (67 percent), the onset of illness occurred between May 1, 1993, and June 30, 1993. The medical records of 17 of the 18 patients were available for review.

Sample Case Report

A 19-year-old man living in rural New Mexico presented to an emergency department with a one-day history of fever, myalgia, chills, headache, and malaise; he did not have dyspnea or cough. The patient had been in excellent health and was a marathon runner; his fiancée, with whom he had lived, had died two days earlier of a rapidly progressive respiratory illness. His temperature was 39.4°C, his heart rate was 118 beats per minute, his blood pressure was 127/84 mm Hg, and his respiratory rate was 24 breaths per minute. The physical examination was normal.

The white-cell count was 7100 per cubic millimeter, with 66 percent segmented neutrophils and 10 percent band forms; the hematocrit was 49.6 percent, and the platelet count was 195,000 per cubic millimeter. The serum creatinine level was 1.1 mg per deciliter (100 μmol per liter), the blood urea nitrogen level was 9 mg per deciliter (3.2 mmol per liter), the serum albumin level was 4.8 mg per deciliter, and the serum lactate dehydrogenase level was 195 IU per liter (normal range, 100 to 190). Urinalysis revealed no protein or blood. Oxygen saturation, determined by pulse oximetry, was 91 percent while the patient was breathing room air, and the chest radiograph was normal. The patient was treated with erythromycin, amantadine, and acetaminophen and then discharged.

Two days later, the patient presented at a clinic with persistent symptoms plus vomiting and diarrhea. His temperature was 36°C, his heart rate was 80 beats per minute, his blood pressure was 90/70 mm Hg, and his respiratory rate was 22 breaths per minute. The physical examination was normal, with clear lung fields on auscultation; the patient was discharged with no change in the diagnosis or therapy. A cough that produced copious yellow sputum, sometimes blood-tinged, and progressive shortness of breath subsequently developed. The day after discharge, the patient had acute respiratory failure and cardiopulmonary arrest and could not be resuscitated. The white-cell count was 65,300 per cubic millimeter, with 45 percent segmented neutrophils and 27 percent band forms. Seven metamyelocytes and 2 myelocytes per 100 cells were noted on review of the differential cell count. The hematocrit was 60.2 percent, and the platelet count was 42,000 per cubic millimeter. The serum creatinine concentration was 2.5 mg per deciliter (220 μmol per liter), the blood urea nitrogen concentration was 32 mg per deciliter (11.4 mmol per liter), the serum lactate dehydrogenase concentration was 1486 IU per liter, and the serum creatine kinase concentration during cardiopulmonary resuscitation was 814 U per liter with an MB fraction of 87 U per liter (11 percent). The chest radiograph showed diffuse interstitial and alveolar infiltrates (Fig. 1).

Clinical Presentation

Among the 17 patients, the mean duration of symptoms before hospitalization was 5.4 days (median, 4; range, 2 to 15). There was no relation between the duration of symptoms at admission and survival ($P = 0.3$). The most common symptoms at the time of hospitalization were fever, myalgia, headache, cough, and nausea or vomiting (Table 1). Myalgia was the most frequently reported initial symptom. Shortness of breath or cough was reported by 13 patients (76 percent) at admission; the cough, which was described as productive by 5 patients, typically preceded respiratory distress. Gastrointestinal symptoms (abdominal pain, nausea and vomiting, or diarrhea) were reported by 13 patients (76 percent); abdominal pain was a prominent symptom in 2. No patient had signs of hemorrhage. Although the diagnosis at the time of admission was pneumonia in 7 patients (41 percent), 10 patients (59 percent) had other diagnoses: abdominal pain in 3 (18 percent); adult respiratory distress syndrome in 2 (12 percent); cardiopulmonary arrest in 2 (12 percent); and sepsis, pyelonephritis, and fever in 1 patient each (6 percent).

Seven patients (41 percent) had underlying illnesses: two had asthma, one had chronic obstructive pulmonary disease and atherosclerotic cardiovascular disease and had undergone a splenectomy, one had a history of silo-filler's disease, two had chronic hypothyroidism, and one had a seizure disorder. Two patients (12 percent) were cigarette smokers, and one had a history of excessive alcohol use. No patients were taking corticosteroids or other immunosuppressive medications.

The most common physical findings were tachypnea and tachycardia (Table 2). Fifty percent of the patients had a respiratory rate of 28 or more breaths per minute, and 50 percent had a heart rate of 120 or more beats per minute. No patient had conjunctival hemorrhage, petechial rash, clinical signs of internal hemorrhage (including a guaiac-positive stool specimen), or peripheral or periorbital edema.

Notable hematologic findings included an elevated white-cell count with increased neutrophils, myeloid precursors, and atypical lymphocytes. Of the 13 patients with differential white-cell counts at the time of admission, 12 (92 percent) had at least 10 percent band forms, 6 (46 percent) had metamyelocytes, and 3 (23 percent) had atypical lymphocytes. Subsequently, metamyelocytes were noted in 11 of 16 patients (69 percent), and atypical lymphocytes in 6 of 16 (38 percent). At the time of admission, the hematocrit was elevated in 13 (76 percent) of the patients (≥50 percent in the men, and ≥45 percent in the women), and the platelet count was less than 150,000 per cubic millimeter in 12 patients (71 percent).

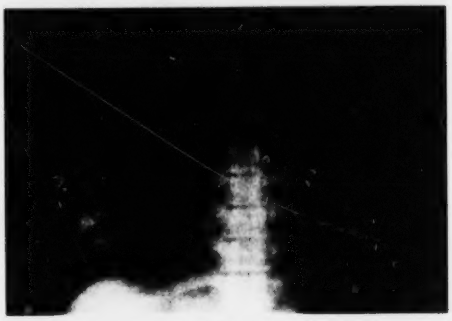

Figure 1. Chest Radiograph Showing Diffuse Interstitial and Alveolar Infiltrates in a Patient with Hantavirus Infection.

The partial-thromboplastin time was 40 seconds or longer in 8 of the 12 patients (67 percent) tested at the time of admission and in 10 of the 12 (83 percent) subsequently (Table 3). Fibrin split products (or D-dimer) and fibrinogen were measured in seven patients: three had elevated D-dimer levels, and all had normal fibrinogen levels.

Five patients had metabolic acidosis with an in-

Table 1. Symptoms in 17 Patients with Hantavirus Infection.

Symptom	No. of Patients (%)
Fever	17 (100)
Myalgia	17 (100)
Headache	12 (71)
Cough	12 (71)
Nausea or vomiting	12 (71)
Chills	11 (65)
Malaise	10 (59)
Diarrhea	10 (59)
Shortness of breath	9 (53)
Dizziness or lightheadedness	7 (41)
Arthralgia	5 (29)
Back pain	5 (29)
Abdominal pain	4 (24)
Chest pain	3 (18)
Sweats	3 (18)
Dysuria or frequent urination	3 (18)
Rhinorrhea or nasal congestion	2 (12)
Sore throat	2 (12)

Table 2. Clinical Findings at the Time of Admission in 17 Patients with Hantavirus Infection.

Sign	Percentage of Patients	Median (Range)
Respiratory rate ≥20/min	100	28 (20–70)
Heart rate ≥100 bpm	94	120 (90–150)
Temperature ≥38.1°C	75	38.8 (35.4–40.4)
Systolic blood pressure ≤100 mm Hg	50	100 (70–130)
Crackles or rales on lung examination	31	
Abdominal tenderness	24	
Cool, clammy, or mottled skin	18	
Injection or suffusion of conjunctiva	18	

creased anion gap at the time of hospitalization. Although minimal abnormalities of renal function were common, serum creatinine levels did not rise above 2.5 mg per deciliter (220 μmol per liter) in any patient (Table 3). The mean (±SD) specific gravity of urine at the time of admission was 1.024±0.010 (median, 1.024; range, 1.006 to 1.040). Six of 15 patients (40 percent) had proteinuria (≥2+) on admission. Urine dipstick tests for blood were positive in 8 of 14 patients (57 percent) tested at the time of admission; microscopical examination showed 0 to 5 red cells per high-power field in 3 patients and 6 to 30 red cells per high-power field in 4.

The initial chest radiograph showed interstitial or interstitial and alveolar infiltrates in 11 patients (65 percent), fluffy alveolar infiltrates in 2 (12 percent), and no abnormalities in 4 (24 percent). Subsequently, 16 patients (94 percent) had rapidly evolving, bilateral, diffuse infiltrates, and 1 patient (6 percent) had interstitial infiltrates confined to the lower lobes. Pleural effusions were noted during the course of the illness in four patients. Eleven of 12 patients (92 percent) who underwent chest radiography and arterial measurement of oxygen saturation at the time of admission had either pulmonary infiltrates or arterial oxygen saturation under 90 mm Hg. In 11 patients, the mean ratio of oxygen tension to inspired oxygen (calculated from the first measurement of arterial blood gas obtained after intubation) was 100 (median, 97; range, 38 to 174).

Table 3. Results of Laboratory Studies during Hospitalization in Patients with Hantavirus Infection.

Test*	Admission Value	Maximal [Minimal] Value
	median (range)	
White cells — $\times 10^{-3}/mm^3$	10.4 (3.1–65.3)	26.0 (5.6–65.3)
Band forms — %	22 (8–62)	27 (4–67)
Hematocrit — %		
Men	51.3 (49.9–60.0)	56.3 (49.9–67.6)
Women	46.4 (35.0–55.8)	48.5 (36.5–60.3)
Platelets — $\times 10^{-3}/mm^3$	84 (26–320)	[64] (12–148)
Prothrombin time — sec	13.0 (11.2–21.1)	14 (12.6–21.1)
Partial-thromboplastin time — sec	42.5 (30.0–150.0)	54.4 (31.0–150.0)
Bicarbonate — mmol/liter	18 (12–25)	[14] (8–20)
Lactate dehydrogenase — IU/liter	362 (209–1525)	568 (324–1525)
Aspartate aminotransferase — IU/liter	112 (28–432)	148 (62–432)
Alanine aminotransferase — IU/liter	55 (25–148)	63 (27–149)
Albumin — g/dl	3.0 (1.5–4.6)	[2.5] (1.5–3.5)
Blood urea nitrogen — g/dl	11 (3–23)	17 (8–32)
Creatinine — mg/dl	1.1 (0.6–2.5)	1.4 (0.6–2.5)
Lactate — mmol/liter	4.4 (2.2–11.0)	—
Creatine kinase — IU/liter†	46 (19–1026)	—

*Maximal normal values: lactate dehydrogenase, 180 to 232 IU per liter; aspartate aminotransferase, 35 to 43 IU per liter; alanine aminotransferase, 35 to 60 IU per liter; lactate, 2.2 mmol per liter; and creatine kinase, 180 to 269 IU per liter. To convert values for blood urea nitrogen to millimoles per liter, multiply by 0.357; to convert values for creatinine to micromoles per liter, multiply by 88.4.

†Two of 10 patients tested had elevated creatine kinase concentrations: 1026 IU per liter with an MB fraction of 16 (2 percent) in 1 patient, and 814 IU per liter with an MB fraction of 87 (11 percent) in another patient, who was undergoing cardiopulmonary resuscitation when the sample was obtained.

Tissue and blood specimens were obtained from the majority of patients for culture, serologic studies, and fluorescent-antibody testing to detect infectious agents. No patient had evidence of infection with other pathogens (Wachsmuth K: personal communication).

Clinical Course

In the group of patients who died, the mean number of days from the onset of symptoms to death was 8 (median, 7; range, 2 to 16). Progressive pulmonary edema and hypoxia requiring intubation and mechanical ventilation developed in 15 patients (88 percent) during the first 24 hours after admission. The clinical course of the illness in patients who did not survive was characterized by pulmonary edema accompanied by severe hypotension (systolic blood pressure less than or equal to 85 mm Hg), frequently terminating with sinus bradycardia, electromechanical dissociation, or ventricular tachycardia or fibrillation. None of the surviving patients had severe hypotension. Hypotension did not appear to be a direct consequence of hypoxia, since several patients with adequate oxygenation had progressive hypotension. Tracheal aspirates of pulmonary secretions from two patients were tested for total protein, albumin, and lactate dehydrogenase concentrations; in both patients the levels were elevated, approaching or exceeding serum levels.

In four of the five patients with Swan–Ganz catheters inserted after the onset of pulmonary edema, the wedge pressure was normal or low and the cardiac indexes were markedly decreased; the fifth patient (58 years old, with a history of atherosclerotic cardiovascular disease and myocardial infarction) had an elevated wedge pressure (Table 4). Information on fluid balance was available for nine patients, seven of whom had a positive balance at the time of death. Two surviving patients who were initially in positive balance underwent spontaneous diuresis during their recovery. Hemodynamic and pulmonary deterioration paralleled the development of metabolic acidosis, rising serum lactate dehydrogenase levels, declining serum albumin levels, prolongation of the prothrombin time and the partial-thromboplastin time, and decreasing platelet counts. With the exception of microscopical hematuria, there were no signs of hemorrhage in any patient.

Pathological Studies

The pathological findings consistently showed large, serous pleural effusions with severe edema of the lungs. No retroperitoneal effusions were present. Microscopical studies of lung tissue showed intraalveolar edema with scant-to-moderate numbers of hyaline membranes and scant-to-moderate numbers of interstitial lymphoid infiltrates (Fig. 2). In well-preserved tissue specimens, pneumonocytes were largely intact, and neutrophils were notably scarce. There was no evidence of a viral cytopathic effect or viral inclusions.

Mild splenomegaly was present in a few patients, although lymphadenopathy was not seen. However, atypical mononuclear cells were consistently seen in the periarteriolar and red-pulp regions of the spleen and in the paracortex of the lymph nodes. In some patients, atypical mononuclear cells were also found in the hepatic triads; in other patients, the liver appeared to be normal. A few patients had small amounts of gastrointestinal hemorrhage. Other viscera, including the kidneys, heart, and brain, were grossly normal and without major microscopical abnormalities.

Predictors of Mortality

A univariate analysis with the use of a logistic model showed no significant correlation between mortality and either symptoms before admission or laboratory abnormalities or physical findings at the time of admission. However, three multivariate logistic models with measurements obtained during hospitalization showed a significant association between mortality and the following combinations of maximally increased laboratory values: the hematocrit and lactate dehydrogenase level ($P<0.005$), the hematocrit and partial-thromboplastin time ($P<0.002$), and the white-cell count and partial-thromboplastin time ($P<0.002$). All three models predicted mortality with 100 percent sensitivity and specificity.

DISCUSSION

Illness resulting from infection with this newly described member of the genus hantavirus is typically severe, characterized by prodromal fever, myalgia, and other symptoms followed by pulmonary edema and hypotension. Because of the characteristically prominent pulmonary involvement, we have designated this illness the hantavirus pulmonary syndrome. The main distinguishing feature of this syndrome is noncardiogenic pulmonary edema. Although an infrequent complication of previously described hantavirus infections, pulmonary edema has been associated with a high rate of mortality.[12,13] The case fatality rate was 76 percent in our series (83 percent of the deaths occurred within nine days after the onset of symptoms), as compared with 5 to 15 percent for severe hemorrhagic fever with renal syndrome and 1 percent for disease due to the Puumala virus.[14]

Table 4. Results of Initial Hemodynamic and Pulmonary Studies in Five Patients.*

PATIENT NO	CARDIAC INDEX	SYSTEMIC VASCULAR RESISTANCE	PCWP	PEAK INSPIRATORY PRESSURE	PULMONARY-ARTERY PRESSURE†	OUTCOME
	liters/min/m^2	dyn · sec · cm^{-5}	mm Hg	cm H_2O	mm Hg	
1	1.9	1268	8	32	29/16	Survived
2	3.5	812	2	33	11/6	Survived
3	1.6	2701	7	31	38 (mean)	Died
4	1.9	1857	5	NA	46 (mean)	Died
5	1.8	1598	28	30	33/16	Died

*PCWP denotes pulmonary-capillary wedge pressure, and NA not available.

†Pulmonary-artery pressure is expressed as systolic/diastolic pressure.

The most likely explanation for the pulmonary findings is an increased permeability of the pulmonary capillaries. An immunohistochemical analysis revealed widespread endothelial distribution of viral antigen in the lungs, kidneys, heart, pancreas, adrenal glands, and skeletal muscle (CDC: unpublished data). The pulmonary manifestations of hantavirus pulmonary syndrome may be due to a direct cellular effect of viral infection, the presence of viral antigen in pulmonary-capillary endothelium, or a virus-induced immune-mediated response. There is evidence of a widespread increase in vascular endothelial permeability in patients with hemorrhagic fever with renal syndrome.[15,16] Whether the pulmonary edema associated with hantavirus pulmonary syndrome is a manifestation of a localized pulmonary process or of a more widespread increase in vascular permeability is unclear. The absence of edema in other tissue on clinical examination and at autopsy suggests

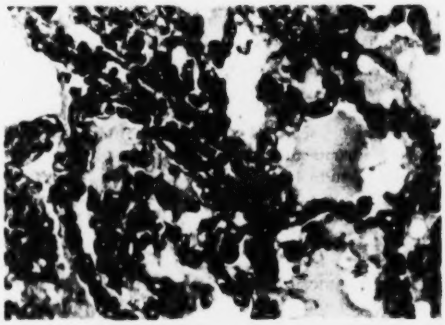

Figure 2. Lung-Tissue Specimen from a Patient with Hantavirus-Associated Interstitial Pneumonitis.

The specimen shows minimal or moderate interstitial lymphoid-cell infiltrates, congestion, and intraalveolar edema (hematoxylin and eosin, ×285).

that the process is localized. Findings that are consistent with a systemic process, however, include the distribution of viral antigen and atypical mononuclear cells throughout the body and the occurrence of proteinuria and hematuria, suggesting renal vascular involvement.

The absence of a marked local response of the pulmonary inflammatory cells distinguishes this syndrome from a variety of other infectious processes. Although the pulmonary findings meet the current criteria for adult respiratory distress syndrome,[17,18] the atypical histopathologic features, including minimal numbers of neutrophils within the alveolar or interstitial spaces, minimal alveolar epithelial disruption, and limited hyaline-membrane formation, may indicate a distinct pathogenesis.[19,20] Although all the patients with severe disease had abnormal oxygenation, hemodynamic deterioration and death occurred in several patients whose arterial oxygen tension had been adequately maintained.

Many early symptoms of hantavirus pulmonary syndrome are also seen in hemorrhagic fever with renal syndrome. Abdominal pain, which can mimic an acute abdomen, is a prominent feature of hemorrhagic fever with renal syndrome and was present in four of the patients with hantavirus pulmonary syndrome. In patients who have hemorrhagic fever with renal syndrome, severe pain in the abdomen, back, and costovertebral angle is thought to be due to extensive extravasation of plasma into the retroperitoneal and peritoneal spaces,[11] which was not seen at postmortem examination in the patients we studied. In two of our patients with abdominal pain, computed tomographic scanning or ultrasound examination did not show abnormal fluid collection in the retroperitoneal space or elsewhere. Renal involvement was minimal, and none of our patients had the marked proteinuria followed by oliguria and renal insufficiency that is characteristic of severe hemorrhagic fever with renal syndrome.[5,13] Similarly, our patients did not have erythematous flushing, periorbital edema, severe costovertebral-angle tenderness, or such hemorrhagic manifestations as petechial and conjunctival hemorrhage, all of which are commonly seen in patients who have hemorrhagic fever with renal syndrome.

Laboratory features common to hantavirus pulmonary syndrome and hemorrhagic fever with renal syndrome include leukocytosis with increased myeloid elements and atypical lymphocytes, hemoconcentration, thrombocytopenia, coagulopathy, decreased serum protein concentrations, and proteinuria.[21,22] In hemorrhagic fever with renal syndrome, coagulopathy has been associated with disseminated intravascular coagulation and hemorrhage.[23] Although three of the patients with hantavirus pulmonary syndrome had evidence of increased fibrinolysis, their fibrinogen levels were normal, and with the exception of microscopical hematuria, signs of hemorrhage were not observed. Elevated serum lactate dehydrogenase and aminotransferase concentrations were common in our series and have been reported previously in patients with hantavirus infection.[12]

Currently, no combination of symptoms, signs, or routine laboratory tests can reliably establish or eliminate the diagnosis of hantavirus infection in people with characteristic clinical signs and symptoms of that illness. Although an elevation of the serum lactate dehydrogenase concentration can be a nonspecific indicator of cellular death, an elevated hematocrit and a prolonged partial-thromboplastin time may be more directly related to the pathophysiology of hantavirus infection.

The initial clinical experience suggests that the key components of therapy for patients with hantavirus infection are maintenance of adequate oxygenation and careful monitoring and support of hemodynamic functioning. Pressor or inotropic agents should be administered in combination with careful volume replacement to treat symptomatic hypotension or shock while avoiding volume expansion and overhydration.

An understanding of the pathophysiology of hantavirus infection, especially the mechanisms underlying the increase in pulmonary and systemic endothelial permeability and vascular tone, may lead to targeted therapeutic interventions. Although data are being collected on the role of immunologic therapy and mediators of inflammation and vascular function in patients with the adult respiratory distress syndrome and septic shock,[24] little information has been published on this approach to the treatment of hantavirus infection.[25,26] In one controlled study of patients who had hemorrhagic fever with renal syndrome, intravenous administration of the antiviral agent ribavirin reduced mortality when the drug was given early in the course of the illness.[27] Since June 4, 1993, intravenous ribavirin has been available through an investigational protocol to treat patients with possible hantavirus infection.

Hantaviruses have been isolated from several species of rodents found in both rural and urban settings in the United States.[28-30] Human infection with these viruses has also been documented,[31] although the seroprevalence data suggest that humans in the United States have a low risk of infection.[32,33] Cases of hantavirus infection continue to be identified, however, and the geographic area where infections occur is expanding. As of December 31, 1993, 53 cases of hantavirus pulmonary syndrome in 14 states have been confirmed.[34] Until the epidemiology of this infection is better understood, prevention strategies, such as behavioral or lifestyle modification and control of rodents, will continue to be based on the epidemiology of other hantavirus infections.[35]

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Appendix

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Lead Poisoning From Mobilization of Bone Stores During Thyrotoxicosis

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We describe a case of thyrotoxicosis accompanied by markedly elevated blood lead levels (initially 53 μg/dl) in a 37-year-old woman. No current source of lead exposure was found; the woman gave a history indicative of lead exposure as a child and as an adult 7 years previously, however. In addition, she was found to have markedly elevated bone lead levels, as measured by K-x-ray fluorescence (154 ± 5 in the mid-tibia and 253 ± 6 μg/g bone mineral in the patella), and an increased serum osteocalcin level (2.76 nmol/l), reflecting the increased bone turnover that often accompanies hyperthyroidism. During treatment with propylthiouracil, serial observations demonstrated a decline in serum osteocalcin that paralleled a decline in blood lead levels. Bone lead levels did not change appreciably. The patient also continued to have lingering neuropsychological symptoms consistent with chronic lead effects. We suggest that increased bone turnover accompanying thyrotoxicosis led to clinically significant lead poisoning in this patient, due to mobilization of accumulated bone lead stores acquired many years earlier. This phenomenon raises the general issue of more subtle forms of lead exposure from increased bone turnover states (e.g., osteoporosis). © 1994 Wiley-Liss, Inc.

Key words: X-ray fluorescence, occupational exposures, thyroid dysfunction, neuropsychological symptoms, bone lead, lead

INTRODUCTION

After inhalation or ingestion, lead enters the bloodstream and is distributed to soft tissues such as blood, brain, and kidney, and then to bone, leading to adverse health effects such as anemia, central nervous system dysfunction, and reproductive system toxicity [Landrigan, 1989]. After heightened exposure to lead ceases, soft tissue stores of lead deplete readily, predominantly through renal excretion, whereas lead accumulated in bone remains for years [Nilsson et al., 1989]. Concerns have

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been raised regarding the potential of lead toxicity to occur from mobilization of these bone stores during times of increased bone turnover, such as pregnancy, lactation, and other hypermetabolic states [Silbergeld, 1991]. We describe the presentation, evaluation, and treatment of a patient with lead poisoning, no identifiable ongoing lead exposure, high skeletal lead as noted by K-X-ray fluorescence (K-XRF, an in vivo method of accurately quantitating bone stores), and marked hyperthyroidism.

Case Report

Initial presentation. A 37-year-old woman employed as a salesperson in a clothing store experienced persistent fatigue, insomnia, difficult concentrating, abdominal cramps, weight loss, muscle and joint aching, and tremor for several months. After reading newspaper reports on lead poisoning, she wondered if her symptoms might be related to work she last performed 7 years earlier, when she removed paint during the course of renovating houses. She requested a blood lead tests from an otolaryngologist who was treating her for an ear infection. The physician found that her chemistry screen (glucose, liver function tests, blood urea nitrogen, creatinine, calcium, and phosphorus) was normal, but that she had an elevated blood lead level of 2.46 μmol/l (51 μg/dl) and an elevated erythrocyte protoporphyrin (EP) level of 0.78 μmol/l (44 μg/dl; normal <0.62 μmol/l or 35 μg/dl).

She was referred to an occupational medicine specialist (R.H.G.). Detailed questioning did not reveal any sources of recent lead exposure. Her two teenage children who lived with her were asymptomatic and had blood leads less than .19 μmol/l (4 μg/dl).

Seven and 10 years previously she had assisted with the deleading of two homes. For a total of about 6 months she scraped and sanded lead paint, wore no respiratory protection, and smoked and ate at the work site. She also recalled that as a child she lived in an old house, frequently chewed on woodwork, windowsills, paper, and pencils, and had chronic abdominal complaints and anemia. She did not recall having a blood lead test as a child. She was held back for 1 year in school because of "math problems."

Her medical history was notable only for symptoms of Raynaud's phenomenon, for which she briefly had taken verapamil without relief. She smoked one pack of cigarettes daily and denied any regular alcohol ingestion.

On physical examination she appeared clinically hyperthyroid, with a regular pulse of 112, blood pressure of 130/60 mm Hg, diffusely enlarged and tender thyroid gland, marked "lid lag," fine resting tremor of both hands, and symmetric hyperreflexia. She also had difficulty replicating Bender diagrams.

The blood lead level, which was measured by flameless atomic absorption spectroscopy in an OSHA-approved laboratory (Bioran, Inc.), was 2.56 μmol/l (53 μg/dl). The EP level, which was measured by hematofluorometry (ESA Labs, Inc.), was 0.66 μmol/l (38 μg/dl). The serum thyroxine (T_4) was >257 nmol/l (>20 μg/dl; normal 64–154 nmol/l), the triiodothyroxine (T_3) uptake was 39.9% (normal 30–40%), free thyroxine (free T_4) was 108 pmol/l (8.4 ng/dl; normal 9.0–22), and thyroxine stimulating hormone was (TSH) <0.05 mIU/l (normal 0.46–3.59). The blood urea nitrogen was 6.1 mmol/l (17 mg/dl), and the serum creatinine 61.9 μmol/l (0.7 mg/dl). The hematocrit was 39.6% and the hemoglobin was 133 g/l (13.3 g/dl). No basophilic stippling was seen on a blood smear. A 24-hour radioactive iodine uptake scan revealed a diffusely enlarged and hyperactive thyroid, consistent with Grave's disease. Antithyroid globulin and antithyroid microsomal antibodies were not detected. The serum osteocalcin level was elevated to 2.76 nmol/l (16.0 ng/ml; normal 0.28–1.59 nmol/l or 1.6–9.2 ng/ml), indicating increased bone turnover [Slovik et al., 1984].

Bone lead measurements were taken of the patient's mid-tibial shaft and patella using a sensitive K-X-ray fluorescence (K-XRF) instrument [Burger et al., 1989] and revealed mid-tibial shaft and patella bone lead levels of 154 ± 5 and 253 ± 6 μg/g bone mineral, respectively (Fig. 1). The levels that would have been expected for a woman of her age who did not have an unusual history of lead exposure are approximately 5 and 10 μg Pb/g bone mineral, respectively [Hu et al., 1990, 1991].

Clinical course. The patient was started immediately on propranolol, which helped control her symptoms of jitteriness, tremor, palpitations, and agitation. One week later she began 800 mg of propylthiouracil daily; 7 weeks after her initial occupational medicine (OM) visit she received 26.1 mCi of I^{131} for thyroid ablation therapy. Her blood lead levels declined as the hyperthyroidism came under better control (Fig. 1). She became hypothyroid and levothyroxine was begun and gradually increased to a daily dose of 125 μg.

At week 36 of observation, 25 weeks after thyroid ablation therapy, the patient was clinically euthyroid, the blood lead level 0.92 μmol/l (19 μg/dl; Table 1 and Fig. 1), and osteocalcin was within the normal range (1.96 nmol/l or 11.4 ng/ml). Bone lead stores were essentially unchanged at 40 weeks. Yet symptoms of profound fatigue, decreased memory recall and concentration abilities, irritability, and feelings of sadness continued. Neurobehavioral assessment using a neurotoxicological oriented detailed test battery [White et al., 1992] identified problems on cognitive tracking tasks requiring mentally holding and manipulating information and on tests of manual motor manipulation and speed. Visuospatial skills were also inferior to verbal abilities. Minnesota Multiphasic Personality Inventory responses suggested that the patient had many physical symptoms and complaints, and that she was suffering from some anxiety and depression. Overall, the pattern of test findings suggests a deficit in nonverbal processing accompanied by manual motor deficits.

One year after her diagnosis, the patient still complained of fatigue, insomnia, irritability, and decreased ability to concentrate, in addition to low-grade headache and nausea. The T_4 was 121 nmol/l with the patient on 150 μg of synthroid daily. Blood lead and EP levels were 0.82 μmol/l (17 μg/dl) and 0.21 μmol/l (12 μg/dl), respectively.

DISCUSSION

This case is important because it demonstrates lead poisoning in the absence of an ongoing source of external lead exposure in a hyperthyroid patient, detects elevated bone lead stores through K-X-ray fluorescence, demonstrates increased bone turnover through elevated serum osteocalcin levels, and documents a decline in blood lead without the use of chelating agents as hyperthyroidism and bone turnover come under control.

This patient's bone lead levels were very high. Her history suggests that they probably derived from remote childhood exposures and 6 months of adult exposure as a lead paint remover. However, her tibia lead levels are comparable to those seen

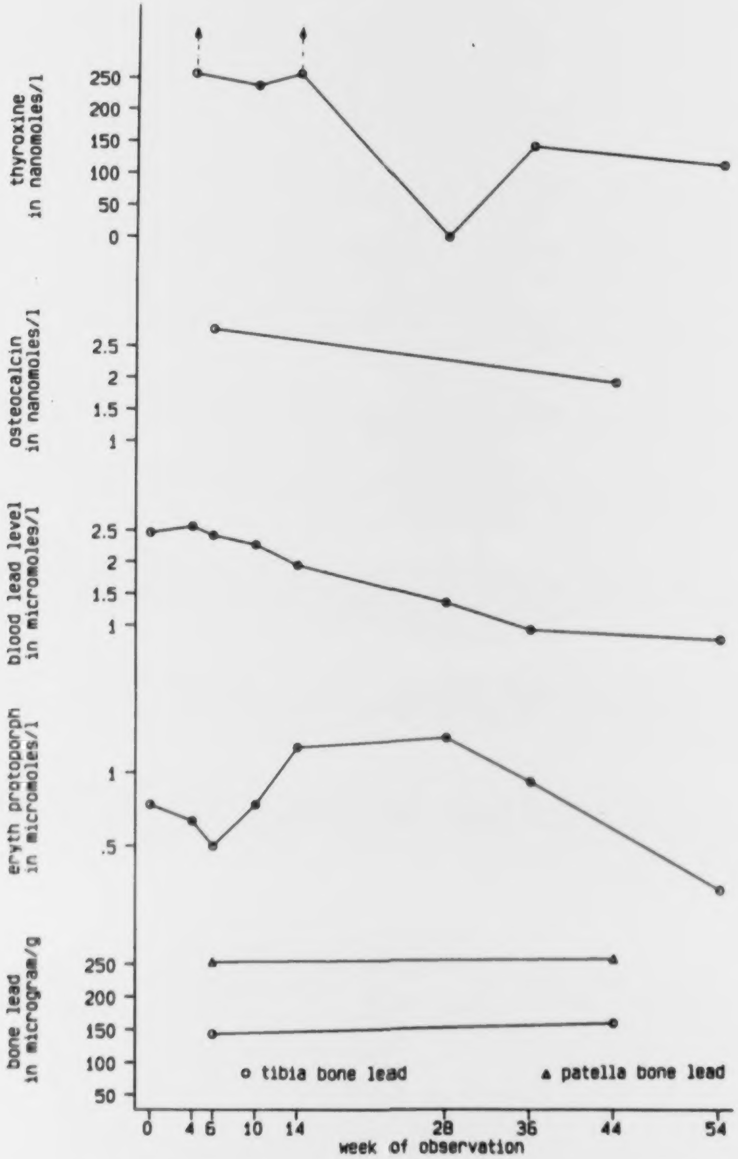

Fig. 1. Serial studies of laboratory data. Therapy with propylthiouracil was begun on week 4; radioactive thyroid ablation was performed on week 11. Normal upper limit levels: thyroxine = 154 nmol/l; osteocalcin = 1.59 nmol/l; erythrocyte protoporphyrin (eryth protoporph) = 0.62 µmol/l; patella lead = 30 µg/g, tibia lead = 20 µg/g. There are no "normal" levels of lead, a xenobiotic. The Centers for Disease Control has established 0.48 µmol/l (10 µg/dl) as the tolerable upper limit for lead in a child's blood, whereas the Occupational Safety and Health Administration does not allow a worker to return to work until his/her blood lead level is below 1.93 µmol/l (40 µg/dl).

TABLE I. Serial Laboratory Values in a 37-Year-old Woman

Laboratory	Normal range	Week of observation								
		0	4	6	10	14	28	36	44	54
Thyroxine (nmol/l)	64–154	—	>257	—	238	>257	<3.7	147	—	121
Osetocalcin (nmol/l)	0.28–1.59	—	2.76	—	—	—	—	—	1.96	—
Blood lead (μmol/l)	<1.21	2.46	2.56	2.41	2.26	1.93	1.35	0.92	—	0.82
Eryth. Protop. (μmol/l)	<0.62	0.78	0.66	0.50	0.80	1.17	1.24	0.94	—	0.21
Tibia bone lead (μg/g)	<20	—	—	154	—	—	—	—	160	—
Patella bone lead (μg/g)	<30	—	—	253	—	—	—	—	258	—

Eryth. protop. = erythrocyte protoporphyrin.

among male workers with several decades of lead exposure [El-Sharkawi et al., 1986; Hu et al., 1991]. This raises the possibility that the patient's lead exposure occurred when she was undergoing rapid bone deposition (e.g., the skeletal growth of adolescence), thereby leading to unusually high bone lead levels. Clarification of this issue will await additional studies of bone lead and exposure.

We believe that the patient's high blood lead levels resulted from increased bone turnover and mobilization of her bone lead stores due to hyperthyroidism. Thyroxine and triiodothyronine stimulate osteoclastic activity and bone resorption, although their precise mode of action is unknown [Mundy, 1990]. Hyperthyroidism, whether endogenous or exogenous, has been found to cause osteoporosis [Fallon, 1983]. This reasoning prompted us to treat this patient's hyperthyroidism (and increased bone turnover) to lower her blood lead, without the use of additional chelating agents, particularly since a blood lead of 50 μg/dl is usually associated with little or no clinical symptoms in adults.

A case has previously been described of lead poisoning in a young patient who had a retained bullet in his leg for over 3 years [Cagin et al., 1978]. Upon developing hyperthyroidism, he was found to have a blood lead level >100 μg/dl. Bone lead content measured by chemical analysis of a bone biopsy sample was 207 μg/g (wet bone, presumably). This level decreased as his hyperthyroidism and lead poisoning were treated with propylthiouracil *and* chelating agents.

Case reports have also described lead poisoning, in the absence of ongoing lead exposure, associated with other physiologic states that are accompanied by increased bone turnover, such as pregnancy [Thompson et al., 1985], chemotherapy [El-Sharkawi et al., 1986; Tothill et al., 1989; Beaney et al., 1990], and tumorous infiltration of bone [Brown and Tompsett, 1945].

Significantly increased blood lead levels have been noted in epidemiological studies of postmenopausal women [Silbergeld et al., 1988]. Given the size of her lead burden, the patient in this case may be at risk for lead intoxication again when she enters the postmenopausal period, possibly exacerbated by l-thyroxine therapy.

This case also raises the issue of long-term health effects associated with lead poisoning. The deficits seen in this patient's test performance were determined to be longstanding because the visuospatial deficits seen occurred across tasks (not just on complex constructional tests such as Block Designs, which might be seen in adult lead exposure) [White et al., 1990] and because the patient's performance on arithmetic knowledge closely paralleled that seen on visuospatial tasks, a correlation often seen developmentally [Rourke, 1985]. In addition, the identification of manual motor and cognitive abnormalities despite normalization of thyroid status is consistent with a longstanding rather than acute process.

Lead exposure was thought to be the etiology of the deficits observed in this patient for several reasons. This patient's results, which included problems with all types of visuospatial tasks and cognitive tracking but not short-term memory or attention, are typical of those seen in children with acute lead exposure and adults with histories of childhood plumbism [White and Proctor, 1992; Feldman and White, 1992]. In addition, bilateral manual motor deficits were seen, which are more consistent with lead as an etiology than other diagnostic possibilities in this patient (such as an idiopathic learning disability). Thyroid dysfunction does not explain the behavioral findings because thyroid function was stable at the time of testing and because her capacity for consistent sustained attention was intact. Finally, test results cannot be explained on the basis of depression because she did not show any of the performance problems which explain deficits in neurobehavioral performance among depressives (i.e., generalized slowing across all tasks, inconsistent attention, or hypoarousal).

Finally, this case demonstrates the clinical utility of a K-XRF instrument for the in vivo measurement of bone lead stores when one suspects a significant internal source of lead exposure. This instrument, recently developed for in vivo measurements, uses a ^{109}Cd gamma-ray source to provoke the emission of fluorescent photons from target tissue; these photons are detected and counted in a back-scatter geometry [Hu et al., 1989]. The number of lead fluorescent photons is compared with the number of photons from the coherent scatter signal, which comes principally from calcium hydroxyapatite; thus the unit of measurement is micrograms of lead per gram of bone mineral (μg/g). This method of normalization renders the measurement insensitive to variations in bone shape, size, density, and histomorphometry, overlying tissue thickness, and movement [Somervaille et al., 1985]. Validation studies of the current instrument in comparison to chemical analysis in cadaveric studies have indicated a high degree of precision and accuracy [Burger et al., 1990; Hu et al., 1990].

This patient remembered pica as a child, but was not known to have had childhood plumbism. X-ray fluorescence was critical in establishing very high bone stores suggestive of childhood lead poisoning. In a study of adults with medical documentation of hospitalization for childhood lead poisoning, 37% were unaware of this history [Hu, 1991].

Given the toxic potential of bone lead stores demonstrated by this case study, the continued lowering of the amount of lead exposure that has been associated with significant health effects in recent research, and the continued widespread nature of lead exposure in the U.S. [ATSDR, 1988], some combination of K-XRF and blood lead testing may eventually become an important screening procedure for select populations of individuals such as patients with thyroid disorders, women contemplating pregnancy, and patients with clinical syndromes suggestive of a low-level lead effect.

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ATSDR **Revised September 1992**

Case Studies in Environmental Medicine

1

Lead Toxicity

Environmental ALERT . . .

☑ ***Children of all races and ethnic origins are at risk of lead poisoning throughout the United States.***

☑ ***In addition to renal disease, cardiovascular effects, and reproductive toxicity, lead may cause irreversible neurologic damage.***

☑ ***Blood lead levels once considered safe are now considered hazardous, with no known threshold.***

☑ ***Lead poisoning is a wholly preventable disease.***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. See page 27 for more information about continuing medical education credits and continuing education units.

Guest Contributor: Sarah E. Royce, MD, MPH
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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

A hyperactive 5-year-old with disturbed hearing and hypochromic anemia

A 5-year-old boy is brought to your office by his mother, who is concerned that her child is hyperactive. At a parent-teacher conference last week, the kindergarten teacher said that the boy seems impulsive and has trouble concentrating, and recommended evaluation by a physician as well as by the school psychologist. The mother states that he has always seemed restless and easily distracted, but that these first 6 months in kindergarten have been especially trying.

Family history reveals that the boy lives with his sister, mother, and maternal grandparents in an older suburb of your community. The child's monthly weekend visits to his father's house are working out fine. However, he seems to be fighting more with his sister, who has an attention-deficit disorder and is repeating first grade. Since the mother moved in with her parents after her divorce 4 years ago, she has worked with the grandfather in an automobile radiator repair shop, where her children often come to play after school. She was just laid off, however, and expressed worry about increasing financial dependence on her parents. She also worries that the grandfather, who has gout and complains increasingly of abdominal pain, may become even more irritable when he learns that she is pregnant. Her third child is due in 4 months.

On chart review, you see that the boy was last seen in your clinic for his preschool physical 1 year ago, results of which were normal. A note describes a very active 4-year-old who could dress himself without help but could not correctly name the primary colors. His vision was normal, but hearing acuity was below normal, and speech and language were slightly delayed. Immunizations are up to date.

Further history on that visit indicated adequate diet, with no previous pica. Spun hematocrit was diminished at 30%. Peripheral blood smear showed hypochromia and microcytosis. There was no evidence of blood loss, and stool examination was negative for occult blood. The diagnosis was "mild iron deficiency anemia," and iron therapy was prescribed. The family failed to keep several follow-up appointments, but the child did apparently complete the prescribed 3-month course of iron supplements. He receives no medications at this time and has no known allergies.

On physical examination today, you note that the boy is in the tenth percentile for height and weight. His attention span is very short, making him appear restless, and he has difficulty following simple instructions. Except for language and social skills, he has reached most important developmental milestones.

Pretest

(a) What should be included in this boy's problem list?

(b) List several possible causes for the anemia.

(c) What tests would you order to confirm or rule out your diagnosis?

Answers are incorporated in Challenge answers (11) through (14) on page 25.

Who's at Risk

- ☐ **Young children have a great potential for lead exposure and are especially susceptible to its toxic effects.**
- ☐ **Since blood lead readily crosses the placenta, lead poses a substantial threat to the developing fetus.**
- ☐ **Workers may bring lead dust home on skin and clothes and unknowingly expose family members.**

By and large, children show a greater sensitivity to lead's effects than adults do. The incomplete development of the blood-brain barrier in very young children (up to 36 months of age) increases the risk of lead's entry into the developing nervous system, which can result in prolonged neurobehavioral disorders. Children absorb and retain more lead in proportion to their weight than do adults. Young children also show a greater prevalence of iron deficiency, a condition that can increase gastrointestinal absorption of lead.

No economic or racial subgroup of children is free from the risk of having blood lead levels high enough to cause adverse health effects. In 1984, approximately 17% of children in the United States were estimated to be at risk of lead poisoning. Sizable numbers of children from families with incomes well above the poverty line have been reported to have elevated blood lead levels. The prevalence of elevated levels, nevertheless, remains highest among inner-city, underprivileged children who live in deteriorating pre-1970s housing containing leaded-paint surfaces. Lead in paint and lead in soil and dust are the principal sources of exposure.

The percentage of African-American children affected by lead is disproportionate to their number in the U.S. population. In 1984 African-American children constituted 46% of the children at risk. The family income categories of these children show that the higher percentage is related to economic factors. African-American children are over represented in the poor and low-income groups as well as in inner-city areas. Other minorities are similarly affected; 15% of Mexican-Americans and 20% of Puerto Rican-Americans exceed a blood lead cutoff of 15 µg/dL. As blood lead levels in the general population are declining because of restrictions on leaded gasoline use, race and income will become better indicators of the likelihood of exposure to leaded paint and, consequently, elevated blood lead levels.

Since lead readily crosses the placenta, the fetus is at risk. Fetal exposure can cause potentially adverse neurologic effects *in utero* and during postnatal development. According to the Public Health Service, in 1984, more than 400,000 fetuses were exposed to lead through maternal blood lead concentrations associated with early developmental effects.

More than 1 million workers in over 100 different occupations may be exposed to lead. In lead-related industries, workers not only may inhale lead dust and lead oxide fumes, but may eat, drink, and smoke in or near contaminated areas, increasing the probability of lead ingestion. If showers and changes of clothing are not provided, workers can bring lead dust home on their skin, shoes, and clothing, thus inadvertently exposing family members.

Challenge

(1) Who else in the family or community discussed in the case study is at risk of lead poisoning?

(2) Evaluate the exposure potential and risk to the fetus mentioned in the case study.

Exposure Pathways

Lead is a naturally occurring element that has been used almost since the beginning of civilization. Because of the many industrial activities that have brought about its wide distribution, lead is ubiquitous in the environment today. All humans have lead in their bodies, primarily as a result of exposure to manmade sources.

☐ **The primary sources of environmental exposure to lead are leaded paint, auto emissions, and drinking water.**

Today, the major environmental sources of metallic lead and its salts are paint, auto exhaust, food, and water. For children, the most important pathways are ingestion of chips from lead-painted surfaces, inhalation of lead from automobile emissions, food from lead-soldered cans, drinking water from lead-soldered plumbing, and medications in the form of folk remedies.

☐ **A wide variety of workers, hobbyists, and substance abusers may encounter potentially high levels of lead. Certain folk remedies may also cause lead poisoning.**

Automobile emissions have been an important source of lead exposure for urban residents, particularly in areas with congested traffic. Although inhalation of lead from gasoline is no longer considered a public health problem, the lead from dust in automobile emissions has been deposited in the soil. Children playing near roads and freeways may come in contact with contaminated soil.

The lead content of paint was not regulated until 1977. Many older structures, residential and commercial, have leaded paint that is peeling, flaking, and chipping. Children can ingest loose paint as a result of pica (compulsive eating of nonfood items) and through mouthing of items contaminated with lead from paint, dust, and soil. High levels of lead in soil and house dust have been associated with increased blood lead levels in children.

☐ **Lead enters the body primarily through ingestion and inhalation.**

Food may contain lead from the environment or from containers. Agricultural vehicles are not required to use unleaded gasoline; consequently, lead can be deposited on and retained by crops, particularly leafy vegetables. Acidic foods have been found to leach lead from lead solder in cans and lead glazes used in making pottery and ceramicware. Water from leaded pipes, soldered plumbing, or water coolers is another potential source of lead exposure. Stationary or point sources of lead include mines and smelters.

Several folk remedies used in this country have been shown to contain large amounts of lead. Two Mexican folk remedies are *azarcon* and *greta*, which are used to treat "empacho," a colic-like illness. *Azarcon* and *greta* are also known as *liga, Maria Luisa, alarcon, coral*, and *rueda*. Lead-containing remedies and cosmetics used by some Asian communities are *chuifong tokuwan, pay-loo-ah, ghasard, bali goli*, and *kandu*. Middle Eastern remedies and cosmetics include *alkohl, kohl, surma, saoott*, and *cebagin*.

In addition to these environmental sources, many occupations, hobbies, and other activities result in potential exposures to high levels of lead and can put the entire family at risk of lead poisoning. Sources of lead exposure are listed below. Lead-glazed pottery, particularly if it is imported, is a potential source of exposure that is often overlooked. Even "safe" ceramicware can become harmful; dishwashing may chip or wear off the protective glaze and expose lead-containing pigments.

Inorganic lead enters the body primarily through inhalation and ingestion and does not undergo biologic transformation. In contrast, organic lead, found primarily in gasoline as tetraethyl lead, enters the body through inhalation and skin contact and is metabolized in the liver. In 1976 and in 1984, federal regulation drastically reduced the amount of lead in gasoline, and today organic lead in gasoline is not as great an environmental concern in the United States as it is in other countries, where it remains a serious hazard.

Sources of lead exposure

Occupational

- Plumbers, pipe fitters
- Lead miners
- Auto repairers
- Glass manufacturers
- Shipbuilders
- Printers
- Plastic manufacturers
- Lead smelters and refiners
- Police officers
- Steel welders or cutters
- Construction workers
- Rubber product manufacturers
- Gas station attendants
- Battery manufacturers
- Bridge reconstruction workers
- Firing range instructors

Environmental

- Lead-containing paint
- Soil/dust near lead industries, roadways, lead-painted homes
- Plumbing leachate
- Ceramicware
- Leaded gasoline

Hobbies and Related Activities

- Glazed pottery making
- Target shooting at firing ranges
- Lead soldering (e.g., electronics)
- Painting
- Preparing lead shot, fishing sinkers
- Stained-glass making
- Car or boat repair
- Home remodeling

Substance Use

- Folk remedies
- "Health foods"
- Cosmetics
- Moonshine whiskey
- Gasoline "huffing"

Challenge

(3) The case study suggests several sources of lead in the boy's life. What are these sources? What questions will you ask to gauge the extent of the boy's exposure to each of these sources?

(4) What questions will you ask the family to evaluate less obvious, but possible, sources of lead exposure?

Biologic Fate

☐ **Once in the bloodstream, lead is primarily distributed among three compartments—blood, soft tissue, and mineralizing tissue. The bones and teeth of adults contain more than 95% of total lead in the body.**

☐ **In times of stress, the body can mobilize lead stores, thereby increasing the level of lead in the blood.**

☐ **The body accumulates lead over a lifetime and normally releases it very slowly.**

In the human body, inorganic lead is not metabolized but is directly absorbed, distributed, and excreted. The rate at which lead is absorbed depends on its chemical and physical form and on the physiologic characteristics of the exposed person (e.g., nutritional status and age). Inhaled lead deposited in the lower respiratory tract is completely absorbed. The amount of lead absorbed from the GI tract of adults is typically 10% to 15% of the ingested quantity; for pregnant women and children, the amount absorbed can increase to as much as 50%. The quantity absorbed increases significantly under fasting conditions and with iron or calcium deficiency.

Once in the blood, lead is distributed primarily among three compartments—blood, soft tissue (kidney, bone marrow, liver, and brain), and mineralizing tissue (bones and teeth). Mineralizing tissue contains about 95% of the total body burden of lead in adults.

The lead in mineralizing tissues accumulates in subcompartments that differ in the rate at which lead is resorbed. In bone, there is both a labile component, which readily exchanges lead with the blood, and an inert pool. The lead in the inert pool poses a special risk because it is a potential endogenous source of lead. When the body is under physiologic stress such as pregnancy, lactation, or chronic disease, this normally inert lead can be mobilized, increasing the lead level in blood. Because of these mobile lead stores, significant drops in a person's blood lead level can take several months or sometimes years, even after complete removal from the source of lead exposure.

Of the lead in the blood, 99% is associated with erythrocytes; the remaining 1% is in the plasma, where it is available for transport to the tissues. The blood lead not retained is either excreted by the kidneys or through biliary clearance into the gastrointestinal tract. In single-exposure studies with adults, lead has a half-life, in blood, of approximately 25 days; in soft tissue, about 40 days; and in the nonlabile portion of bone, more than 25 years. Consequently, after a single exposure a person's blood lead level may begin to return to normal; the total body burden, however, may still be elevated.

For lead poisoning to develop, major acute exposures to lead need not occur. The body accumulates this metal over a lifetime and releases it slowly, so even small doses, over time, can cause lead poisoning. It is the total body burden of lead that is related to the risk of adverse effects.

Challenge

(5) What would likely be revealed by an X ray of the abdomen or long bones of a lead-exposed child?

(6) Why does the blood lead level fail to drop within a few days, even with complete removal from the source of exposure?

(7) Several weeks after chelation therapy and removal from the source of exposure, in some cases the patient's blood lead level is found to have increased again. What is the cause of this rebound phenomenon?

Physiologic Effects

Whether lead enters the body through inhalation or ingestion, the biologic effects are the same; there is interference with normal cell function and with a number of physiologic processes. The lowest observable blood lead levels associated with specific health effects in chronically exposed children and adults are shown in Figure 1.

☐ **Lead affects primarily the peripheral and central nervous systems, the blood cells, and metabolism of vitamin D and calcium. Lead also causes reproductive toxicity.**

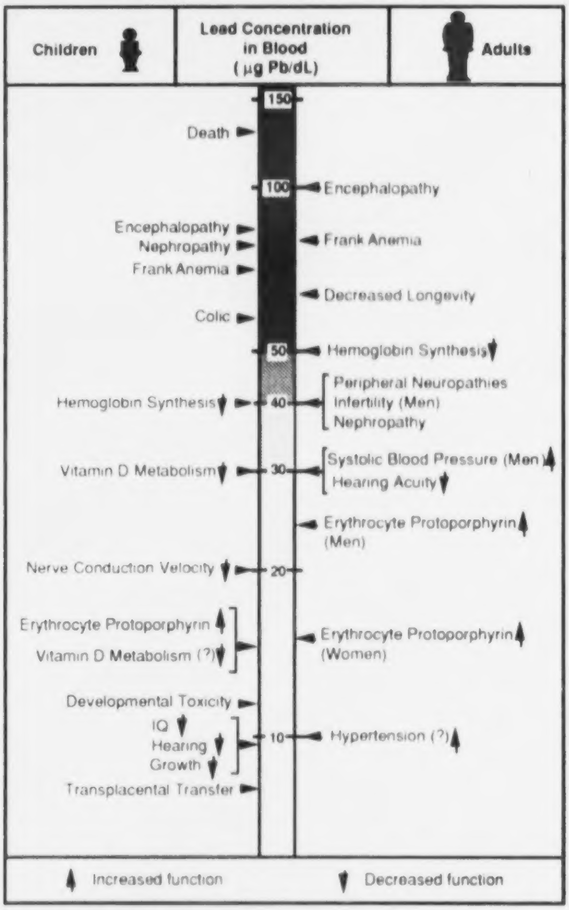
Neurologic Effects

The most sensitive target of lead poisoning is the nervous system. In children, neurologic deficits have been documented at exposure levels once thought to cause no harmful effects. In addition to the lack of a precise threshold, childhood lead toxicity may have permanent effects. One study showed that damage to the central nervous system (CNS) that occurred as a result of lead exposure at age 2 resulted in continued deficits in neurologic development, such as

☐ **Neurologic deficits, as well as other effects caused by lead poisoning, may be irreversible.**

- **Effects in children generally occur at lower blood lead levels than in adults.**
- **The developing nervous system in children can be affected adversely at blood lead levels of less than 10 µg/dL.**

Figure 1. Effects of inorganic lead on children and adults--lowest observable adverse effect levels



Adapted from ATSDR, *Toxicological Profile for Lead* (1989)

lower IQ scores and cognitive deficits, at age 5. In another study that measured total body burden, primary school children with high tooth lead levels but with no known history of lead poisoning had larger deficits in psychometric intelligence scores, speech and language processing, attention, and classroom performance than children with lower levels of lead. A 1990 follow-up report of children with elevated lead levels in their teeth noted a sevenfold increase in the odds of failure to graduate from high school, lower class standing, greater absenteeism, more reading disabilities, and deficits in vocabulary, fine motor skills, reaction time, and hand-eye coordination 11 years later. The reported effects are more likely caused by the enduring toxicity of lead than by recent excessive exposures because the blood lead levels found in the young adults were low (less than 10 micrograms per deciliter [µg/dL]).

Hearing acuity, particularly at higher frequencies, has been found to decrease with increasing blood lead levels. Hearing loss may contribute to the apparent learning disabilities or poor classroom behavior exhibited by children with lead intoxication.

Adults also experience CNS effects at relatively low blood lead levels, manifested by subtle behavioral changes, fatigue, and impaired concentration. Peripheral nervous system damage, primarily motor, is seen mainly in adults. Peripheral neuropathy with mild slowing of nerve conduction velocity has been reported in asymptomatic lead workers. Lead neuropathy is believed to be a motor neuron, anterior horn cell disease with peripheral dying-back of the axons. Frank wrist drop occurs only as a late sign of lead intoxication.

Hematologic Effects

Lead inhibits the body's ability to make hemoglobin by interfering with several enzymatic steps in the heme pathway. Ferrochelatase, which catalyzes the insertion of iron into protoporphyrin IX, is quite sensitive to lead. A decrease in the activity of this enzyme results in an increase of the substrate, erythrocyte protoporphyrin (EP), in the red blood cells. Recent data indicate that the EP level, which has been used to screen for lead toxicity in the past, is not sufficiently sensitive at lower levels of blood lead and is therefore not as useful a screening test for lead poisoning as previously thought. (See Laboratory Evaluation for further discussion of EP testing.)

- ☐ **Lead inhibits several enzymes that are critical to the synthesis of heme.**
- ☐ **Lead poisoning in children only rarely results in anemia.**

Lead can induce two types of anemia. Acute high-level lead poisoning has been associated with hemolytic anemia. In chronic lead poisoning, lead induces anemia by both interfering with erythropoiesis and by diminishing red blood cell survival. It should be emphasized, however, that anemia is not an early manifestation of lead poisoning and is evident only when the blood lead level is significantly elevated for prolonged periods.

Endocrine Effects

☐ **Lead interferes with a hormonal form of vitamin D, which affects multiple processes in the body, including cell maturation and skeletal growth.**

A strong inverse correlation exists between blood lead levels and levels of vitamin D. Because the vitamin D-endocrine system is responsible in large part for the maintenance of extra- and intracellular calcium homeostasis, it is likely that lead impairs cell growth and maturation and tooth and bone development.

Renal Effects

☐ **Lead-induced chronic renal insufficiency may result in gout.**

A direct effect on the kidney of long-term lead exposure is nephropathy. Impairment of proximal tubular function manifests in aminoaciduria, glycosuria, and hyperphosphaturia (a Fanconi-like syndrome). There is also evidence of an association between lead exposure and hypertension, an effect that may be mediated through renal mechanisms. Gout may develop as a result of lead-induced hyperuricemia, with selective decreases in the fractional excretion of uric acid before a decline in creatinine clearance. Renal failure accounts for 10% of deaths in patients with gout.

Reproductive and Developmental Effects

☐ **Maternal lead stores readily cross the placenta, placing the fetus at risk.**

An increased frequency of miscarriages and stillbirths among women working in the lead trades was reported as early as the turn of the century. Although the data concerning exposure levels are incomplete, these effects were probably a result of far greater exposures than are currently found in lead industries. Reliable dose-effect data for reproductive effects in women are still lacking today.

Increasing evidence indicates that lead not only affects the viability of the fetus, but development as well. Developmental consequences of prenatal exposure to low levels of lead include reduced birth weight and premature birth. Lead is an animal teratogen; however, most studies in humans have failed to show a relationship between lead levels and congenital malformations.

The effects of lead on the male reproductive system in humans have not been well characterized. The available data support a tentative conclusion that testicular effects, including reduced sperm counts and motility, may result from chronic exposure to lead.

Carcinogenic Effects

☐ **EPA's Science Advisory Board has recommended that lead be considered a probable human carcinogen.**

Case reports have implicated lead as a potential renal carcinogen in humans, but the association remains uncertain. Soluble salts, such as lead acetate and lead phosphate, have been reported to cause kidney tumors in rats.

Challenge

(8) *What are the major effects of lead on the human body?*

(9) *How do lead's effects differ in children and adults?*

Clinical Evaluation

History and Physical Examination

Medical evaluation of a patient with suspected lead exposure includes a full workup and medical history. Clues to potential exposure are often obtained by discussing the following with the family:

occupational history of all home occupants
family history, including use of unusual medicines
location, age, and physical condition of residence, school, day-care center, etc
home remodeling activities
condition of household pets
hobbies of all family members
use of imported or glazed ceramics
drinking water source and type of pipe
nutritional status
proximity to industrial facilities and hazardous waste sites

☐ **The first signs of lead poisoning in children are often subtle neurobehavioral problems that adversely affect classroom behavior and social interaction.**

☐ **Speech or hearing impairments, or both, are not uncommon in lead-exposed children.**

The physical examination should include special attention to the hematologic, cardiovascular, gastrointestinal, and renal systems. The nervous system, including behavioral changes, should be carefully evaluated. A purplish line on the gums (lead line) is rarely seen today, but if present, usually indicates severe and prolonged lead poisoning.

For children, hearing, speech, and other developmental milestones should be carefully evaluated and documented. In certain geographic areas, iron deficiency is common in children 9 to 24 months of age. Since iron and calcium deficiencies are known to enhance the absorption of lead and to aggravate pica, it is especially important to assess the nutritional status of young children.

Signs and Symptoms

Because of differences in individual susceptibility, symptoms of lead intoxication and their onset may vary. With increasing exposure, the severity of symptoms can be expected to increase. Those symptoms most often associated with varying degrees of lead toxicity are listed below. In symptomatic lead intoxication, blood lead levels generally range from 35 to 50 µg/dL in children and 40 to 60 µg/dL in adults. Severe toxicity is frequently found in association with blood lead levels of 70 µg/dL or more in children and 100 µg/dL or more in adults.

☐ **Most persons with lead toxicity are not overtly symptomatic.**

Continuum of signs and symptoms associated with lead toxicity

Mild Toxicity	Moderate Toxicity	Severe Toxicity
Myalgia or paresthesia	Arthralgia	Paresis or paralysis
Mild fatigue	General fatigue	Encephalopathy—may abruptly lead to seizures, changes in consciousness, coma, and death
Irritability	Difficulty concentrating	Lead line (blue-black) on gingival tissue
Lethargy	Muscular exhaustibility	Colic (intermittent, severe abdominal cramps)
Occasional abdominal discomfort	Tremor	
	Headache	
	Diffuse abdominal pain	
	Vomiting	
	Weight loss	
	Constipation	

Some of the hematologic signs of lead poisoning mimic other diseases or conditions. In the differential diagnosis of microcytic anemia, lead poisoning can usually be ruled out by obtaining a venous blood lead concentration; if the blood lead level is less than 25 µg/dL, the anemia usually reflects iron deficiency or hemoglobinopathy. Two rare diseases, acute intermittent porphyria and coproporphyria, also result in heme abnormalities similar to those of lead poisoning.

Other effects of lead poisoning can be misleading. Patients exhibiting neurologic signs due to lead poisoning have been treated only for peripheral neuropathy or carpal tunnel syndrome, delaying treatment for lead intoxication. Failure to correctly diagnose lead-induced gastrointestinal distress has led to inappropriate abdominal surgery.

Laboratory Evaluation

If pica or accidental ingestion of lead-containing objects (such as curtain weights or fishing sinkers) is suspected, an abdominal radiograph should be taken. Hair analysis is not usually an appropriate assay for lead toxicity because no correlation has been found between the amount of lead in the hair and the exposure level. The probability of environmental lead contamination of a laboratory specimen and inconsistent sample preparation make the results of hair analysis difficult to interpret. Suggested laboratory tests to evaluate lead intoxication include the following:

CBC with peripheral smear
Blood lead level
Erythrocyte protoporphyrin level
BUN and creatinine level
Urinalysis

CBC with Peripheral Smear. In a lead-poisoned patient, the hematocrit and hemoglobin values may be slightly to moderately low. The differential and total white count may appear normal. The peripheral smear may be either normochromic and normocytic or hypochromic and microcytic. Basophilic stippling is usually seen only in patients who have been significantly poisoned for a prolonged period. Eosinophilia may appear in patients with lead toxicity but does not show a clear dose-response effect.

☐ **Basophilic stippling is not always seen in lead-poisoned patients.**

☐ **The best screening and diagnostic test for lead poisoning is a blood lead level.**

Blood Lead Level. A blood lead level is the most useful screening and diagnostic test for lead exposure. A blood lead level reflects lead's dynamic equilibrium between absorption, excretion, and deposition in soft- and hard-tissue compartments. For chronic exposures, blood lead levels often underrepresent the total body burden; nevertheless, it is the most widely accepted and commonly used measure of lead exposure. Blood lead levels respond relatively rapidly to abrupt or intermittent changes in lead intake (for example, ingestion of lead paint chips by children) and, within a limited range, bear a linear relationship to those intake levels.

Lead is most harmful to children under 6 years of age. Every child who has a developmental delay, behavioral disorder, or speech impairment, or who may have been lead-exposed, should be considered for a blood lead test. Equally important, siblings, housemates, and playmates of children with suspected lead toxicity probably have similar exposures to lead and should be promptly screened. For occupationally exposed adults, consult the federal lead standard for the mandated type and frequency of lead screening (p. 20, Workplace, Air).

Today, the average blood lead level in the U.S. population is below 10 µg/dL, down from an average of 16 µg/dL (in the 1970s), the level before the legislated removal of lead from gasoline. A blood lead level of 10 µg/dL is about 3 times higher than the average level found in some remote populations.

The levels defining lead poisoning have been progressively declining. (See Biologic Guidelines in Standards and Regulations.) Currently, the consensus level of concern for children is 10 to 14 µg/dL (see Table 1). Effects on stature have been reported to begin at levels as low as 4 µg/dL, the present limit for accurate blood lead measurement. Taken together, effects occur over a wide range of blood lead concentrations, with no indication of a threshold. No safe level has yet been found for children. Even in adults, effects are being discovered at lower and lower levels as more sensitive analyses and measures are developed.

☐ **Using an EP or ZPP assay to screen children for lead poisoning is not as useful as once thought.**

EP and ZPP Levels. Until recently, the test of choice for screening asymptomatic children and other populations at risk was erythrocyte protoporphyrin (EP), commonly assayed as zinc protoporphyrin (ZPP). An elevated level of protoporphyrin in the blood is a result of accumulation secondary to enzyme dysfunction in the erythrocytes. It reaches a steady state in the blood only after the entire population of circulating erythrocytes has turned over, about 120 days. Consequently, it lags behind blood lead levels and is an indirect measure of long-term lead exposure.

Table 1. Interpretation of blood lead test results and follow-up activities: class of child based on blood lead concentration

Class	Blood lead concentration (μg/dL)	Comment
I	< 9	A child in Class I is not considered to be lead-poisoned.
IIA	10-14	The presence of many children (or a large proportion of children) with blood lead levels in this range should trigger communitywide childhood lead poisoning prevention activities. Children in this range may need to be rescreened frequently.
IIB	15-19	A child in Class IIB should receive nutritional and educational interventions and more frequent screening. If the blood lead level persists in this range, environmental investigation and intervention should be done.
III	20-44	A child in Class III should receive environmental evaluation and remediation and a medical evaluation. Such a child may need pharmacologic treatment of lead poisoning.
IV	45-69	A child in Class IV will need both medical and environmental interventions, including chelation therapy.
V	> 70	A child with Class V lead poisoning is a medical emergency. Medical and environmental management must begin immediately.

The major disadvantage of using EP (ZPP) testing as a method for lead screening is that it is not sensitive at the lower levels of lead poisoning. Data from the second National Health and Nutrition Examination Survey (NHANES II) indicate that 58% of 118 children with blood lead levels above 30 μg/dL had EP levels within normal limits. This finding shows that a significant number of children with lead toxicity would be missed by reliance on EP (ZPP) testing alone as the screening tool. An EP (ZPP) level is still useful in screening patients for iron deficiency anemia.

Normal values of ZPP are usually below 35 μg/dL. Hyperbilirubinemia (jaundice) will cause falsely elevated readings when the hematofluorometer is used. EP is elevated in iron deficiency anemia and in sickle cell and other hemolytic anemias. In erythropoietic protoporphyria, an extremely rare disease, EP is markedly elevated (usually above 300 μg/dL.)

BUN, Creatinine, and Urinalysis. These parameters may reveal only late, significant effects of lead on renal function. Renal function in adults can also be assessed by measuring the fractional excretion of uric acid (normal range 5% to 10%; less than 5% in saturnine gout; greater than 10% in Fanconi syndrome).

☐ **Renal function may be impaired in lead-exposed persons.**

Challenge

(10) What should be included in the problem list for the patient described in the case study?

(11) List several possible causes of the boy's anemia.

(12) You have just learned from the laboratory that the boy has a ZPP level of 350 µg/dL. What are the possible causes of this elevated value?

(13) What other laboratory tests will you now order to confirm or rule out your diagnosis?

Treatment and Management

☐ **All therapeutic chelating agents have potentially adverse side effects and should be used cautiously.**

☐ **The type of therapy required will normally depend on the patient's blood lead level. Asymptomatic patients with blood lead levels below 25 µg/dL usually require only separation from the source of exposure.**

It is not sufficient to provide treatment only; the patient and lead source must be permanently separated. After diagnosing lead poisoning, the physician should call upon the resources of the local health authority to determine the lead source (e.g.,home, workplace). If the lead poisoning is caused by leaded paint in the home, the patient and all other family members should be rehoused until the home has undergone safe and satisfactory lead abatement. Family members and other persons likely to have been exposed should be tested for lead poisoning. Steps should be taken to identify and correct dietary deficiencies, particularly of calcium and iron, and to educate family members on the preventable hazards of lead.

The most reliable index of exposure is a measurement of blood lead concentration. In those asymptomatic children having blood lead levels below 25 µg/dL, treatment is probably not indicated, and removal from the source is the most important action. Patient follow-up to confirm a decreasing blood lead level is needed, however.

☐ **Children with blood lead levels of 45 µg/dL or greater should be referred for appropriate chelation therapy immediately.**

The Centers for Disease Control (CDC) recommends that children with blood lead levels of 45 µg/dL or greater should be referred for appropriate chelation therapy immediately. Some practitioners routinely treat children with blood lead levels between 25 and 44 µg/dL with chelation therapy and some do not use chelating agents for children with blood lead levels in this range. Other practitioners base this decision on the results of a provocative EDTA test. Only very minimal data exist about chelation therapy for children with blood lead levels below 25 µg/dL, and such children should not be chelated except in the context of approved clinical trials.

Several drugs (see Table 2) are used in the treatment of lead poisoning. These drugs, capable of binding or chelating lead, deplete the soft and hard (skeletal) tissues of lead and thus reduce its acute toxicity. All drugs have potential side effects and must be used with caution. In rare cases, the chelating agent, calcium disodium ethylenediaminetetraaceate acid ($CaNa_2EDTA$) has caused proteinuria, microscopic hematuria, proximal tubule damage, hypercalcemia, and fever. Before instituting this therapy or using the chelation challenge test, the patient should be hospitalized and a physician experienced in chelation should be consulted. Such physicians can be identified by contacting an accredited regional poison control center, university medical center, or state or local health department.

☐ **The EDTA challenge test will indicate the extent of lead stores in the body. Some practitioners use this test when deciding whether to institute chelation therapy for a patient with a blood lead level between 25 and 44 µg/dL.**

Table 2. Chelating agents used in treating children who have lead poisoning

Product Name	Generic Name	Chemical Name	Abbreviation
Calcium Disodium Versenate	Edetate disodium calcium	Calcium disodium ethylenediaminetetraacetate	$CaNa_2EDTA$
BAL* in Oil	Dimercaprol	2,3-dimercapto-1-propanol	BAL*
Cuprimine	D-penicillamine	3-mercapto-D-valine	D-penicillamine
Chemet	Succimer	Meso-2,3-dimercaptosuccinic acid	DMSA

* British anti-Lewisite

Challenge

(14) The laboratory results indicate that the blood lead level of the child in the case study is 50 µg/dL. What treatment and follow-up activities will you recommend?

(15) Who could you contact for medical consultation regarding this boy's case?

(16) What can you as a physician do to prevent exposure to lead?

Standards and Regulations

The number of federal standards and regulations reflect the extent to which lead is considered a public health problem. In some cases, the lead levels are mandated; in others, they are only recommended standards (Table 3).

Table 3. Summary of standards and regulations for lead

Agency*	Focus	Level	Comments
CDC	Blood	10 μg/dL	Advisory; level of concern for children†
OSHA	Blood	50 μg/dL	Regulation; medical removal from exposure (See p. 20, Workplace, Air)
OSHA	Air	50 μg/m^3 30 μg/m^3	Regulation; PEL§ (General industry) Action level
ACGIH	Air	150 μg/m^3	Advisory; TLV/TWA¶ (Under revision)
EPA	Air	1.5 μg/m^3	Regulation; 3-month average
CDC (NIOSH).	Air	100 μg/m^3	REL**
EPA	Water	15 μg/L	Action level, (See p. 20, Environment, Water)
FDA	Food	100 μg/day	Advisory
CPSC	Paint	600 ppm (0.06%)	Regulation, by dry weight

* ACGIH = American Conference of Governmental Industrial Hygienists, CDC = Centers for Disease Control, CPSC = Consumer Product Safety Commission, EPA = Environmental Protection Agency, FDA = Food and Drug Administration, NIOSH = National Institute for Occupational Safety and Health, OSHA = Occupational Safety and Health Administration

† If many children in the community have blood lead levels $\geq$ 10 μg/dL, communitywide interventions (primary prevention activities) should be considered by appropriate agencies

§ PEL (Permissible Exposure Limit). The employer shall assure that no employee is exposed to lead at concentrations >50 μg/m^3 of air averaged over an 8-hour period

¶ TLV/TWA (Threshold Limit Value/Time Weighted Average). The time weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect

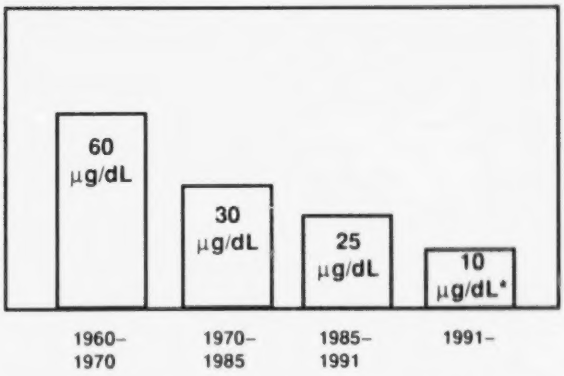
** REL (Recommended Exposure Limit). Air concentration to be maintained so that worker blood lead remains <0.060 mg/100g of whole blood

Biologic Guidelines

Lead levels that in the past were considered safe are now considered hazardous. As new information has emerged about the neurologic, reproductive, and possible hypertensive toxicity of lead, and as more sensitive parameters are developed, the levels defining lead poisoning have been progressively lowered. Between 1986 and 1988, several studies demonstrated neurobehavioral impairment in lead-exposed children with blood lead levels as low as 10 to 14 µg/dL. As more data become available, the definition of lead toxicity level will likely continue to be lowered (Figure 2).

☐ **CDC lowered the recommended action level for lead poisoning in children in 1991.**

Figure 2. CDC's action level for blood lead in children has steadily declined.



* Emphasis is on primary prevention efforts (i.e., elimination of lead hazards before children are poisoned).

Physician Reporting Requirements. Several states require primary care physicians and persons in charge of screening programs to report both presumptive and confirmed cases of lead toxicity to the appropriate health agency so that abatement of the lead source, education of the patient, and remediation steps can be undertaken. In many states, laboratories performing blood lead or EP (ZPP) tests are also required to report abnormal results to the appropriate health agency.

☐ **Several states require primary care physicians to report cases of lead poisoning.**

Workplace

Air

☐ **OSHA has set required standards for the amount of lead allowed in workroom air at 50 μg/m³ averaged over an 8-hour workday.**

The federal lead standard specifies the permissible exposure limit (PEL) of lead in the workplace, the frequency and extent of medical monitoring, and other responsibilities of the employer. The Occupational Safety and Health Administration (OSHA) has set a PEL of lead in workroom air at 50 μg/m³ averaged over an 8-hour workday for workers in general industry. For those exposed to air concentrations at or above the action level of 30 μg/m³ for more than 30 days per year, OSHA mandates periodic determination of blood lead levels. If a blood lead level is found to be greater than 40 μg/dL, the worker must be notified in writing and provided with medical examination. If a worker's blood lead level reaches 60 μg/dL (or averages 50 μg/dL or more), the employer is obligated to remove the employee from excessive exposure, with maintenance of seniority and pay, until the employee's blood lead level falls below 40 μg/dL (29 CFR §1910.1025). A copy of the lead standard can be obtained by calling your regional office of OSHA.

Environment

Air

☐ **EPA will probably lower its present ambient air standard for lead.**

Occupational exposure limits are generally set to accommodate 8-hour workdays and healthy persons; they bear little relation to environmental limits, which are set to protect the most susceptible persons in the general population. EPA requires that the concentration of lead in air the general public may breathe shall not exceed 1.5 μg/m³ averaged over a calendar quarter. This standard will probably be lowered. To reduce the amount of lead released into the environment, EPA regulations now limit the level of lead in unleaded gasoline to 0.05 grams per gallon.

Drinking Water

☐ **EPA's proposed goal for lead in drinking water after treatment is zero.**

EPA estimates that about 20% of the U.S. population (including 3.8 million children) consumes drinking water with lead levels above 20 μg/dL. EPA is required to set drinking water standards with two levels of protection. The primary standards define contaminant levels in drinking water as levels above which the water source requires treatment. These maximum contaminant levels (MCLs) are limits enforceable by law and are set as close as possible to the maximum contaminant level goals (MCLGs), the levels determined to be safe by toxicologic and biomedical considerations, independent of feasibility. EPA has promulgated a final rule for lead in drinking water: this rule does not establish an MCL; the MCLG is zero and the action level is set at 15 μg/L. If more than 10% of targeted tap water samples exceed the action level, certain actions are required of water system administrators. For further information, call the U.S. EPA Safe Drinking Water Hotline toll-free at 1-800-426-4791.

The use of lead solder and other lead-containing materials in connecting household plumbing to public water supplies was banned by EPA as of June 1988. Many older structures, however, still have lead pipe or lead-soldered plumbing internally, which may substantially increase the lead content of water at the tap. Regulations controlling the lead content of drinking-water coolers in schools went into effect in 1989.

Food

Regulating lead contamination in foods is the responsibility of the Food and Drug Administration (FDA). FDA has set a goal of less than 100 µg/day as the total lead intake by children 1 to 5 years of age. Lead in food and beverages is encountered by virtually this entire age group in the United States.

☐ **Most lead in food comes from solder in cans or glazes on ceramicware.**

According to a 1988 ATSDR report, FDA has estimated that about 20% of all dietary lead comes from canned food; about two-thirds of that amount results from lead solder in cans. The number of food cans that are lead-soldered continues to decline. In 1979, over 90% of all food cans were lead soldered; in 1986, this figure was 20%, or less than about 2 million cans. It is important to note that imported canned foods are not included in these figures and may still contain lead. Imported glazed ceramics and lead-containing pottery are also potential sources of dangerously high levels of lead.

Paint

Since 1977, the Consumer Product Safety Commission has limited the lead in most paints to 0.06% (600 ppm by dry weight). Paint for bridges and marine use may contain greater amounts of lead.

☐ **Today, paint intended for residential use is limited to 0.06% lead content.**

Challenge

(17) Regarding the facts reported in the case study, should public health authorities or regulatory agencies be notified? Why?

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(18) You learn from the boy's mother that her place of employment had poor ventilation and no provision for respiratory protection, shower facilities, or work clothes. She ate lunch and smoked in the repair shop. "In fact," she says, "I wonder if my layoff has anything to do with the blood test the company had me get." The company's test indicated that her blood lead level was 62 µg/dL. What advice could you give the boy's mother regarding her former employment?

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Answers to Pretest and Challenge Questions

Pretest questions are found on page 1. Challenge questions begin on page 3.

(1) All members of the family are at risk; they should be promptly evaluated and, if necessary, treated. The mother's unborn child is also at risk. Workers in the radiator repair shop and their families, and any of the children's playmates who have accompanied them to the repair shop after school, should also be screened.

(2) The boy's mother is 5 months pregnant. Since the placenta presents no barrier to lead, the fetus' blood lead level is likely to be similar to that of the mother. It is during the initial weeks of pregnancy that the neurologic system of the conceptus is formed; therefore, damage to the fetus may have already occurred. The mother is no longer working at the repair shop, but you should alert her and the family to the possibility of continued lead exposure via the grandfather, who may be bringing lead dust home on his skin, shoes, or clothes.

(3) Two of the obvious sources of lead suggested in the case study are leaded paint at home (paint flakes, household dust, and soil) and fumes and dust from solder at the radiator repair shop. You should determine if the boy ever had pica (a compulsive eating of nonfood items, to be distinguished from normal hand-to-mouth behavior of children). Pica is more common in children aged 2 to 5, so it is unlikely that this is a present behavior. Exposure to high levels of lead at the radiator repair shop is very possible, and you need to ascertain the type and length of the boy's play at the shop.

(4) To evaluate less obvious, but possible, sources of lead exposure, you might inquire about the proximity of the child's home and play areas to freeways, hazardous waste sites, and industry. The occupations of all adults in the household are important; children of lead-exposed workers have been shown to have higher lead levels than control groups. Do any of the boy's associates or does the father have hobbies involving lead, such as those mentioned on page 4? You might also inquire whether the home is undergoing remodeling, whether any home or folk remedies are used, if glazed ceramicware is used for food, or if there are lead or lead-soldered pipes in the house that could contaminate the drinking water.

(5) If a child does not have pica and there is nothing to suggest that a lead-containing object has recently been ingested, an abdominal X ray will likely be negative. On long-bone radiograms, opacities in the metaphysial plates may be seen after 4-8 weeks or more of lead exposure. These "lead lines" (which are due to dense zones of calcium and not deposited lead) are more likely to be found in larger bones (e.g., radius and tibia) than in smaller bones (e.g., ulna and fibula). Lead lines seen in the smaller bones may be indicative of a longer exposure, usually several months. Radiographs are helpful only in the rare circumstances that they are positive. Negative X rays do not rule out lead poisoning.

(6) Even with complete removal from the source of exposure, the blood lead level will drop only gradually because, without chelation, lead is only slowly excreted. In addition, even as it is excreted, it may be replaced by lead currently stored in bones and teeth.

(7) This rebound phenomenon is due to the mobilization of lead from the body's stores in bones and teeth.

(8) The major effects of lead on the human body are damage to the neurologic, hematologic, renal, and reproductive systems.

(9) Because of an incompletely developed blood-brain barrier, children under 36 months of age are particularly susceptible to neurologic damage at very low blood lead levels. Since children (to age 7) are more sensitive to lead's effects, most adverse effects of lead are often manifested at lower blood lead levels in children than in adults.

(10) History suggests delayed language ability, slightly impaired hearing, short stature, possible attention deficit disorder, and anemia. The child is also experiencing passive exposure to his mother's cigarette smoke and family disruption related to his parents' divorce.

(11) Three of the most common causes of microcytic anemia are iron deficiency, hemoglobinopathy, and lead poisoning. In lead-poisoned patients, anemia is usually evident only when the blood lead level is significantly elevated for prolonged periods. It manifests in only a relatively small number of children with chronic lead poisoning. It is possible for a patient to be both lead-poisoned and to have anemia due to some other cause. The relative rarity of nutritional iron deficiency in this boy's age group and the absence of evidence for blood loss suggest consideration of other etiologies to explain the anemia.

(12) An elevated ZPP level is most often due to iron deficiency anemia, hemolytic anemias, or lead poisoning. A rare disease that may cause the ZPP level to be markedly elevated is erythropoietic protoporphyria.

(13) To confirm lead poisoning, the best test is a venous blood lead level. If the blood lead level is below 25 µg/dL, then a serum ferritin level and other iron studies can be used to determine if iron deficiency anemia exists.

(14) With an elevated blood lead level of 50 µg/dL, the conclusion is that the boy is lead-poisoned. In this case, the child should be referred for appropriate chelation therapy immediately. It is important to immediately identify and eliminate all sources of lead exposure for both the boy and his family. Environmental evaluation, intervention, and remediation should begin immediately. All household members should be screened for lead exposure (See Table 1, page 15). Adequate diet for the family should be stressed.

(15) You should consult with a physician experienced in treating lead-poisoned patients. To identify such physicians, contact your state or local health department, a university medical center, or a certified regional poison control center.

(16) Knowing the subgroups at greatest risk of lead exposure, you should take every opportunity to educate these subpopulations, your colleagues, and the community about the hazards of lead poisoning and the steps to prevent its occurrence. Those children and members of the community whom you suspect may be in danger of lead poisoning should be promptly screened.

(17) In certain states, public health authorities must be notified if a patient's blood lead level and ZPP level exceed certain limits. In any case, you should contact your state or local health department so all sources of lead in the home can be identified and abated. You should also notify OSHA so the radiator repair shop can be brought, if required, into compliance with the federal lead standard. A NIOSH health hazard evaluation could also be requested. The reason for notifying these agencies is to prevent lead exposure in others.

(18) The federal lead standard mandates that a worker with a blood lead level of 60 µg/dL or higher (or an average of 50 µg/dL) undergo medical removal from the lead hazard and be reassigned with retention of job seniority and pay. In addition to referring her for obstetrical evaluation, you should recommend that the mother talk to her employer, employee representative, and OSHA to clarify her work status under the lead standard and possible reinstatement procedures.

Sources of Information

More information on the adverse effects of lead and the treatment and management of lead-exposed persons can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Lead Toxicity* is one of a series. For other publications in this series, please use the order form on the back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of the Director, at (404) 639-6204.

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LEGIONNAIRES' DISEASE

Description of an Epidemic of Pneumonia

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Abstract An explosive, common-source outbreak of pneumonia caused by a previously unrecognized bacterium affected primarily persons attending an American Legion convention in Philadelphia in July, 1976. Twenty-nine of 182 cases were fatal. Spread of the bacterium appeared to be air borne. The source of the bacterium was not found, but epidemiologic analysis suggested that exposure may have occurred in the lobby of the headquarters hotel or in the area immediately surrounding the hotel. Person-to-person spread seemed not to have occurred. Many hotel employees appeared to be immune, suggesting that the agent may have been present in the vicinity, perhaps intermittently, for two or more years. (N Engl J Med 297:1189-1197, 1977)

NEW infectious diseases continue to be found with the aid of increasingly sophisticated laboratory methods for identifying microbial agents. Often, it is through investigation of an epidemic — as recently with Lassa fever[1] and Ebola-virus disease[2] — that new organisms and new diseases are identified. The occurrence of an epidemic signals the need for an investigation of a previously unrecognized problem and presents a cluster of cases in which, by means of appropriate comparisons with controls, a common epidemiologic, clinical, and microbiologic thread can be sought. On the centennial of Koch's discovery that bacteria caused anthrax, an explosive outbreak of pneumonia occurred in Pennsylvania, mostly in persons who had attended an American Legion convention. We describe the epidemic, the clinical illness and, in a companion paper,[3] the evidence that it is caused by a bacterium not previously recognized as a cause of human disease.

BACKGROUND

The 58th annual convention of the American Legion, Department of Pennsylvania, was held in Philadelphia July 21-24, 1976. The headquarters of the convention was in Hotel A. During the same period, the 56th annual convention of the American Legion Auxiliary, Department of Pennsylvania, was also held in Philadelphia, with headquarters in Hotel B. Persons who attended the conventions included American Legion delegates, delegates of the Ladies Auxiliary, members of the families of Legion and Auxiliary delegates, and other Legionnaires with no formal role at the conventions.

Official activities of the American Legion Convention incuded meetings for all delegates, a parade, a testimonial dinner, a dance, committee meetings, regional caucuses and a breakfast. Unofficial activity centered around the Hotel A lobby, a sidewalk in front of the hotel and several hospitality rooms. Each of the 13 candidates for major office reserved a room or a suite of rooms in Hotel A to serve as a hospitality room for entertaining delegates. Each district and many of the local posts had their own hospitality rooms, which were scattered throughout several hotels. Liquor — most commonly beer and whiskey with or without mixers and ice — was served along with simple snacks.

Hotel A was constructed in 1904 and has been extensively modified and renovated since. Hotel guests were housed in approximately 700 rooms on the sec-

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ond through 16th floors. The lobby floor, which is slightly above street level, included a registration desk, a counter for the sale of newspapers and sundries, several shops and airline offices, ladies' and men's rooms and two restaurants and lounges. Meeting rooms were on the first and 18th floors. The air-conditioning system consisted of two water chillers in the subbasement from which chilled water was circulated to approximately 60 air-handling units in the building.

METHODS

Case Definition

A case was considered *Legionnaires' disease* if it met clinical and epidemiologic criteria. The clinical criteria required that a person have onset between July 1 and August 18, 1976, of an illness characterized by cough and fever (temperature of 38.9°C or higher) or any fever and chest x-ray evidence of pneumonia. To meet the epidemiologic criteria, a patient either had to have attended the American Legion Convention held July 21-24, 1976, in Philadelphia or had to have entered Hotel A between July 1 and the onset of the illness. A person was considered to have had *Broad Street pneumonia* if he met the clinical but not the epidemiologic criteria for Legionnaires' disease but had been within one block of Hotel A between July 1 and the onset of illness. A person was considered to have *seroconversion* if there was a fourfold or greater rise in titer to 1:64 or higher by indirect fluorescent-antibody measurement using as antigen the unnamed gram-negative bacterium implicated as the cause of Legionnaires' disease.[3] A person was considered *seropositive* if he had a titer of 1:128 or greater by indirect fluorescent-antibody assay.

Case Finding

Information about cases was obtained through active and passive surveillance. After recognition on August 2 that an outbreak had occurred among those attending the American Legion Convention, the Pennsylvania Department of Health alerted local health officials to help in the investigation. State health officials also notified the Pennsylvania Medical Society, the Pennsylvania Osteopathic Association and the Hospital Association of Pennsylvania of a potential statewide epidemic. They requested co-operation in reporting potential cases, and, because of the statewide nature of the problem, the Pennsylvania Department of Health was made the center for planning and data collection.

Public-health nurses were instructed to search hospitals in their districts for hospitalized Legionnaires. They made daily rounds at local hospitals and reported date of onset of illness, clinical description, association with the convention and existence of secondary spread of illness. A telephone hot line was established in Philadelphia, and the public invited to report possible epidemic cases. News reports were scanned to identify additional cases.

Surveys

Eight epidemiologic surveys are discussed in this paper.

Hotel-guest survey. To assess the rate at which illness meeting the clinical criteria was occurring in hotel guests other than Legionnaires in Philadelphia, a telephone randomized survey was made of guests registered at four hotels between July 6 and August 7. The hotels surveyed included Hotels A and B as well as a center city hotel where a few Legionnaires stayed (Hotel C), and a hotel on the periphery of the city where no Legionnaires stayed (Hotel D). The overall completion rate was 67 per cent; however, there were considerable differences in completion rates within time periods for each hotel and between hotels. An additional group of 80 persons not attending the convention who were registered at Hotel A on July 23 were also selected for interview.

Hotel-employee survey. To determine if illness was affecting employees of the headquarters hotel, a review was made of unscheduled employees' absences since July 1, and each employee who missed two or more days was interviewed concerning illness that might meet the case criteria. In addition, an approximate 25 per cent randomized sample of the estimated 400 employees of Hotel A was selected for telephone questioning. Also, an attempt was made to interview all persons who worked in the lobby.

Roommate survey. Fifty-nine roommates of 52 patients and 69 roommates of 68 control Legionnaires at Hotel A were queried about illness in the interval from July 21 to August 9, 1976.

Hospital survey. To determine if illness meeting the clinical criteria of disease was occurring apart from the American Legion Convention and Hotel A, emergency-room and admission records of patients seen from July 1 to August 9, 1976, in three hospitals serving center-city Philadelphia (Graduate Hospital, Pennsylvania Hospital and Thomas Jefferson University Hospital) were reviewed.

Pneumonia and influenza deaths. Deaths caused by pneumonia and influenza are routinely reported to the Philadelphia City Health Department as part of the national influenza surveillance system. Review was made of reported deaths in the interval from June 4 through September 24 for the years 1974, 1975 and 1976 among Philadelphia residents.

Legionnaire census. On August 9 a packet of two-page questionnaires regarding activities at the convention and subsequent illness was delivered to the commanders of each of the 1002 local American Legion posts in Pennsylvania. Each commander was asked to identify persons in or associated with his post who had attended the convention, to deliver a form to each person and to retrieve completed questionnaires; 3683 forms were returned by Legionnaires who had attended the convention. Of the 3580 who listed their convention status, 1849 (51.6 per cent) were delegates. Because 2274 delegates voted at the convention, it may be estimated that approximately 4400 persons attended the convention $\left(\frac{2274}{1849} \times 3580 = 4403\right)$. The responses of persons who reported having been well since the convention were compared with those of patients.

Case-control survey No. 1. A case-control survey, designed after completion and analysis of the Legionnaire census, was intended for all surviving male Legionnaires on the case list and a randomized sample of 202 men chosen from the Legionnaire census who indicated that they had been well since the convention (controls). Interviews were completed by telephone on August 17 with 147 control Legionnaires (73 per cent) and 113 case Legionnaires (91 per cent).

Case-control survey No. 2. An attempt was made to survey 56 case and 56 control Legionnaires in December, five months after the epidemic. The patients chosen were the surviving male delegates who had been hospitalized and were known to have had a temperature of 38.9°C or higher and radiographic evidence of pneumonia. Controls were matched for age and sex. Fifty-two case and age-matched control pairs were interviewed in person.

Other Technics

Various parts of the inanimate environment of Hotel A were sampled in August to determine if changes in the physical environment of the hotel might have taken place in temporal association with the Legionnaires' convention. Weather records for Philadelphia were reviewed. Selected autopsies were attended by medical epidemiologists to supervise collection of appropriate specimens. Interviews were conducted with residents and workers in the area of Hotel A, with persons attending several other conventions and with officials of the American Legion. Two patients with Legionnaires' disease who had had brief exposure were brought back to the scene of the convention and "walked through" their activities at the time. Medical epidemiologists attempted to interview in person and examine all suspect cases identified as of August 3. Hospital medical records of 94 and 147 hospitalized patients were obtained and reviewed.

Laboratory Methods

The Bureau of Laboratories of the Pennsylvania Department of Health co-ordinated local collection of specimens from all persons. Details of the laboratory aspects of the investigation are presented in a companion paper.[3]

RESULTS

Clinical Illness

Of the 182 patients, 147 (81 per cent) were hospitalized, and 29 (16 per cent) died. The typical illness began seven days after the Legionnaire had arrived at the convention and three days after he had returned home. Earliest symptoms were malaise, muscle aches and a slight headache. Within less than a day there was a rapidly rising fever associated with shaking chills. A nonproductive cough was common early, often with the onset of initial symptoms. Chest pain often accompanied the cough and was frankly pleuritic in a third of the cases. Dyspnea, abdominal pain and gastrointestinal symptoms also occurred in many of the patients. By the time a patient saw his physician, two or three days after onset of illness, the temperature had usually risen to 38.9 to 40.6°C, and examination of the chest disclosed some rales, without evidence of consolidation. One fifth of the patients became obtunded. In most cases the rest of the physical examination gave normal results.

From review of hospital records of 94 of the hospitalized patients it was found that 58 had a history of pre-existing illness including 10 with emphysema or other chronic pulmonary disease, 13 with hypertension, nine with arteriosclerotic cardiovascular disease, seven with peptic-ulcer disease and four with cancer. The admission urinalysis showed a $\geq 3+$ test for protein in 20 per cent of the patients, and microscopic hematuria occurred in 10 per cent. Fifty-nine per cent had a white-cell count above 10,000 per cubic millimeter, but in only 20 per cent was it above 14,000 per cubic millimeter; 50 per cent had a shift to the left, with more than 5 per cent band forms. The initial white-cell count and the proportion of band forms were higher in those who died than in those who survived. A total count less than 2000 per cubic millimeter was seen in two persons who died and in one who survived; only two other patients had fewer than 6000 white cells per cubic millimeter. Erythrocyte sedimentation rate was greater than 80 mm per hour in 33 per cent of those in whom it was measured. Modest elevations of blood urea nitrogen, glutamic oxalacetic transaminase and alkaline phosphatase were commonly seen.

Radiographs of the chest were abnormal in 90 per cent. Patchy, interstitial infiltrates or areas of consolidation were most often seen early and usually progressed to more widespread consolidation. In nearly 50 per cent of the cases, pulmonary infiltrates remained unilateral. Effusions, when present, were usually minimal and did not present management problems. No cavitation was seen.

In most cases the illness progressed over two or three days, and in the survivors there was a remittent fever that broke by lysis. Cough commonly became productive during the course of the illness but was rarely purulent. Most patients were treated with oxygen. Inspired oxygen concentration greater than 40 per cent and mechanical ventilation were required in 20 per cent; these requirements were (not unexpectedly) associated with death. Shock occurred in 50 per cent of those who died and in none of those who recovered. Upper and lower gastrointestinal bleeding was not uncommon but may have been related to the stress of illness. Transient impairment of renal function was frequent and usually mild. In four cases renal failure required treatment with dialysis. One patient had evidence of preceding hypotension and clinical shock before onset of renal failure. Three patients were in renal failure on admission to the hospital and had no antecedent history of hypotension. Death occurred after a median of seven days after onset of illness. Risk of death was increased in older patients. In those who recovered, radiographic evidence of improvement appeared at a median of 10 days after onset of illness and lagged behind clinical resolution.

Individual patients seemed to improve after therapy with a variety of antibiotics was started, but, when cases were considered as a group, no antibiotic was clearly effective. The case-fatality ratio was higher in those treated with cephalothin (20/49) and steroids (14/25), and was intermediate in patients treated with aminoglycosides (9/25), chloramphenicol (3/10), ampicillin (10/41) and penicillin (6/30). Outcome was most favorable in patients given tetracycline (3/30) or erythromycin (2/18). The severity of illness at the time of hospital admission among patients in each treatment group was evaluated by a combination of clinical and laboratory features of prognostic value; this assessment showed the groups to be clinically comparable before therapeutic intervention. The timing of therapy did not confound evaluation of treatment efficacy except in moribund patients treated terminally with steroids.

Pathological findings are described in detail elsewhere.[4] Characteristic findings were largely limited to the lungs, in which pneumonia and acute diffuse alveolar damage were seen.[4] With a silver-impregnation stain, many bacilli were consistently seen in affected alveoli. Other stains commonly used did not demonstrate large numbers of bacilli. Serologic data appear in the paper by McDade et al.[3] In summary, 91 per cent (101 of 111) of patients with Legionnaires' disease from whom adequate serum specimens were obtained either showed seroconversion (56 per cent) or were seropositive only (35 per cent). Nine of 14 cases of Broad Street pneumonia in which adequate serum specimens were obtained four to seven months after the epidemic showed seroconversion or seropositivity.

Some Legionnaires had mild respiratory illness that did not meet the clinical criteria for Legionnaires' disease. Of delegates responding to the Legionnaire census, 98 not meeting the criteria reported fever and either cough or a chest x-ray examination since the convention. No properly timed serum pairs are available from these persons. Serum specimens drawn on August 6 and September 1, 1976, from 21 Legionnaires who had attended the convention and who were subsequently perfectly well did not show a fourfold change in titer. Mild respiratory illness not meeting the clinical criteria was not appreciably more common in registrants of Hotel A or B in the week of July 18-24 than in registrants of Hotels C or D (data not shown).

Person, Place and Time

Of the 182 cases meeting the clinical and epidemiologic definition of Legionnaires' disease, 142 were in males. Patients ranged in age from three to 82 years; 75 per cent were 40 to 69 years old, with a mean of 54.7 years. One hundred and forty-nine had attended the American Legion Convention (Table 1). One case was in a hotel employee. Of the other 32 patients nine had attended the Eucharistic Congress (August 1-8, 1976), two a Candlemakers' Convention (July 17-21, 1976), and one a Magicians' Convention (July 14-17); the others had no convention association. Eighty-four of the patients and 75 of the Legionnaire patients had stayed overnight at Hotel A.

The incidence rate of illness among those at the American Legion Convention, calculated from the Legionnaire census, was 4.0 per cent. Among delegates the rate was 6.8 per cent, among family members 6.3 per cent and among others attending the Legion convention 0.4 per cent (Table 1). Only two of the 17 family members who were ill (12 per cent) returned a questionnaire in the Legionnaire census, as compared with 72 (58 per cent) of 125 delegates with illness, suggesting that completion rates in family members were lower than those in delegates. If there had been a fourfold underestimation of the denominator in family members, their actual attack rate would have been approximately 1.6 per cent — a rate closer to that of Auxiliary and other nondelegates. Incidence rates were 5.4 per cent for men and 1.9 per cent for women. Attack rate for delegates increased progressively with increasing age (Table 2). The homes of ill persons were scattered throughout Pennsylvania, and the rates of illness were similar for Legionnaires coming from Philadelphia or the remaining eastern, western, and central parts of the State (data not shown).

Table 1. Attack Rates of Legionnaires' Disease among Persons at the American Legion Convention, July 21–24, 1976, According to Status.

CONVENTION STATUS	ATTACK RATE (%)	RESPONDENTS	NO. OF CASES
Delegate	6.8	1,849	125
Auxiliary	0.6	701	4
Family member	6.3	268	17
Nondelegate	0.4	762	3
Unknown	0	103	0
Totals	4.0	3,683	149

Thirty-nine persons met the criteria of Broad Street pneumonia. Ages of persons with Broad Street pneumonia ranged from 19 to 70 years, with a mean of 50.6 years. Twenty-four cases were in males. Five cases were fatal. Eight of these persons were known to have walked on the same side of Broad Street as Hotel A, 13 on the other side of the street, and two on both sides of the street; information is not available on the other 16. Five persons admitted to some contact with Legionnaires during the convention; six had attended the Eucharistic Congress.

Table 2. Legionnaires' Disease Attack Rates in American-Legion Delegates, According to Age and Residence at Hotel A or Elsewhere, July 21–24, 1976.

AGE (YR)	HOTEL A RESIDENTS			RESIDENTS ELSEWHERE			TOTAL RESIDENTS		
	ILL	TOTAL	% ILL	ILL	TOTAL	% ILL	ILL	TOTAL	% ILL
<40	3	44	6.8	3	116	2.6	6	160	3.7
40–49	9	160	5.6	11	232	4.7	20	392	5.1
50–59	27	320	8.4	25	523	4.8	52	843	6.2
60–69	12	108	11.1	19	207	9.1	31	315	9.8
≥70	11	54	20.4	5	76	6.5	16	130	12.3
Unknown	0	2	0	0	7	0	0	9	0
Totals	62	688	9.0	63	1,161	5.4	125	1,849	6.8

Illness meeting the clinical criteria was rare except in Hotels A and B in the week of the American Legion Convention (Table 3). Five persons who met the clinical criteria for a case of Legionnaires' disease were found among registrants at Hotels C and D during the week surveyed, two during the week before the American Legion Convention, and three during the week of the convention. Three of the five entered Hotel A and met epidemiologic criteria for Legionnaires' disease.

There was no evidence from the survey of hotel guests that an epidemic associated with hotel residence continued after the American Legion cohort. For Hotel A in the week of July 18-24, a supplementary sample was chosen of persons who had no known association with the convention. Including the supplementary group, illness in those who attended the convention (15 of 110) was more common than that in those who did not (one of 47) among registrants in Hotel A on the nights of July 21-23.

Only one of more than 400 employees, an air-conditioner repairman, met the case criteria with a temperature of 38.9°C and cough beginning on July 24 that required him to miss work for four days. His two children, three and four years old, had colds beginning on July 27, and his wife became ill on August 2. He recovered and did not see a physician or have a chest x-ray study. No serum specimens were available from him or his family. Nine other employees who worked in different locations in the hotel were known to have had minor colds but did not meet the case criteria.

Table 3. Illness Resembling Legionnaires' Disease in Randomized Sampling of Guests in Four Philadelphia Hotels According to Week of Registration, July 6–August 7, 1976.

HOTEL	7/6–7/10	7/11–7/17	7/18–7/24	7/25–7/31	8/1–8/7
A	0/142/155*	0/130/159	15/180/200	0/106/152	0/88/147
B	—	—	5/144/200	—	—
C	—	1/70/85	2/100/160	0/95/140	0/78/160
D	—	1/90/151	1/84/150	0/92/151	0/58/154

*No. ill/no. interviewed/no. chosen for survey.

The epidemic curve showed a rapid upswing in cases from July 22 to 25, followed by a plateau through July 28, and a somewhat slower decline through August 3; a scattering of cases were observed until August 16 (Fig. 1). The 149 cases in Legionnaires showed dense clustering in a narrow space of time, whereas the 33 cases in non-Legionnaires were clustered in two groups from July 24 to August 1 and August 9 to 16. The distribution of cases of Broad Street pneumonia was similar to that of Legionnaires' disease.

The distribution in time of illnesses between July 1 and August 9 that were found in the hospital survey gave no evidence of an unusual incidence of disease about the time of the outbreak of Legionnaires' disease (data not shown). There was no increase in the weeks of or after the outbreak in the number of persons diagnosed on death certificates in Philadelphia as having died from pnuemonia or influenza (data not shown).

Incubation Period

For the 72 patients with Legionnaires' disease or Broad Street pneumonia who either were culture positive or showed seroconversion (Fig. 2), a comparison of date of onset with dates of possible exposure within one block of Hotel A permits an estimate of the possible or necessary range of incubation period. All but two cases could be explained by an incubation period of two to 10 days. The two exceptions (Cases 68 and 58) apparently had incubation periods of 16 and 26 days, respectively. The two are residents of the same town. 64 km from Philadelphia.

Time of Exposure

The 72 persons with Legionnaires' disease or Broad Street pneumonia who were shown to have seroconversion or from whom the agent of Legionnaires' disease was cultured, 67 attended the American Legion Convention or were in or in the vicinity of Hotel A in the interval July 1 through July 24 (Fig. 2). Single days of exposure on July 21, 22 and 23 were associated with seroconversion. Four other patients were in the vicinity in the first nine days of August. The person who was the last case (Case 58) was present in Philadelphia only on July 5 and fell ill 26 days later.

Place of Exposure

When responses of all ill and well Legionnaires were compared, attendance at each of many conven-

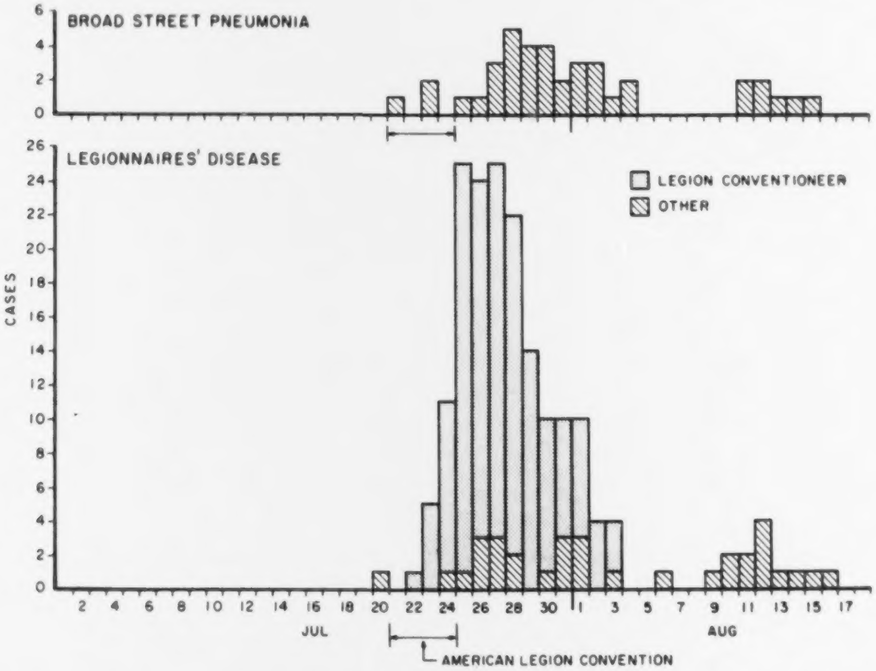

Figure 1. Dates of Onset of Illness in Cases of Legionnaires' Disease and Cases of Broad Street Pneumonia in Philadelphia, July 1-August 18, 1976.

Dates of onset of two cases of Legionnaires' disease are unknown.

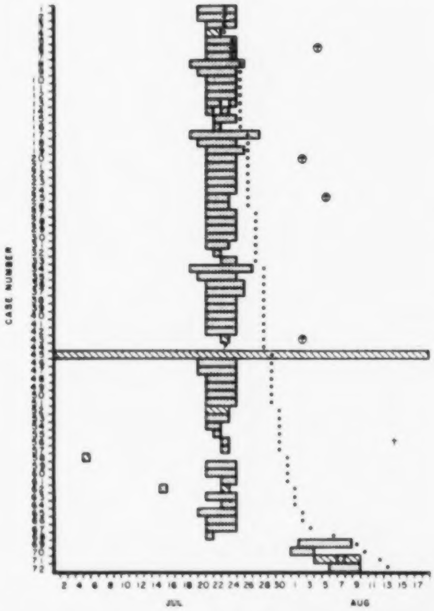

Figure 2. Days Spent at Hotel A or the American Legion Convention (□) or Otherwise within One Block of Hotel A (▨) by Each of 72 Persons Who Met the Clinical Definition of Legionnaires' Disease or Broad Street Pneumonia and Who Were Shown to Have Seroconversion or a Positive Culture for the Implicated Gram-Negative Bacterium.

One person with an uncertain date of exposure within one block of Hotel A is shown (?). Also shown are dates of the onset of illness (●), of death (†) and of positive culture (○).

tion activities was associated with illness. These associations were with the typical activities of delegates and could have been expected because delegates formed the group at highest risk of disease. To avoid the confounding effect of the high risk for delegates, most subsequent analysis of places of exposure and modes of spread is restricted to Legionnaire delegates.

From the Legionnaire census, 62 (50 per cent) of 125 ill delegates resided at Hotel A as compared with 356 (35 per cent) of 1006 well delegates ($P<0.01$ by chi-square). Illness was not associated with residence at any other hotel. Cases did not cluster within Hotel A by location of bedroom.

Among delegates responding to the Legionnaire census, significantly more patients than controls attended hospitality room A on the 14th floor ($P<0.05$ by chi-square). All other rooms showed no significant differences between case and control delegates. The mean number of hospitality rooms attended by delegates determined from the Legionnaire census was 2.8 for ill delegates and 1.8 for well ($P<0.02$ by t-test). The difference was observed only for delegates who did not stay at Hotel A. No association was found between illness and consumption of specific foods or ice served in common in several hospitality rooms. Five of the 12 family members who were ill and from whom information was available and none of those who had Broad Street pneumonia attended hospitality rooms.

The mean number of minutes spent in the lobby of Hotel A by Legionnaire patients (delegates and nondelegates) was greater than that for controls, both for residents of Hotel A (259 and 142, respectively) and for Legionnaires who stayed elsewhere (133 and 86, respectively). Case delegates spent more time than controls in the lobby of Hotel A, both among residents of Hotel A ($P = 0.05$ by Mann-Whitney test) and among delegates who stayed elsewhere ($P<0.001$ by Mann-Whitney test).

Case delegates who were serologically positive or had seroconversion spent more time on the average than control delegates in Hotel A on July 23 (82 per cent of case delegates and 54 per cent of controls spent more than six hours in the hotel on that day; $P<0.0001$ by chi-square). On July 23, among these serologically confirmed case delegates, there was a linear trend for more time spent on the sidewalk in front of Hotel A as compared to controls ($P = 0.04$ by chi-square). Among persons who watched the Legion parade on July 23, independent of hotel of residence, those with serologically confirmed cases were more likely than controls to have watched from the sidewalk directly in front of Hotel A (55 per cent vs. 26 per cent, $P<0.01$ by chi-square).

Single serum specimens were obtained from 61 employees of Hotel A on August 19 and 20, 1976. Indirect fluorescent-antibody titers to the agent of Legionnaires' disease were <1:64-34, 1:64-17, 1:128-7, 1:256-2 and 1:1024-1. These titers contrast with those of 30 employees of the Pennsylvania State Health Laboratory in North Philadelphia, all of whom had titers <1:64. Among Hotel A employees, titers of ≥1:64 were found in a larger proportion of persons whose employment there had begun before 1975 (20 of 34, or 59 per cent) than in those who began work later (six of 25, or 24 per cent) ($P<0.05$ by chi-square). The date on which two persons started work was unknown. There was no association between titer and age, shift, type or location of work within the hotel, or illness between July 1 and August 19, 1976.

Mode of Transmission

Investigation of the mode of transmission included the following general categories: person-to-person, food, tobacco, alcohol, water, animals, ice, fomites and air.

Person-to-person. In the case-control survey No. 1, completed on August 17, 24 days after the end of the convention, none of the contacts (140 adults and 53 children) with Legionnaires' disease who were interviewed had contracted illness that met the clinical criteria for a case. Similarly, among family contacts (143 adults and 68 children) of well attendants at the convention, none had had illness after the convention that met the clinical criteria.

There was no clustering of cases in rooms as might be expected if person-to-person spread occurred. Room-mates of patients had an attack rate of 8.5 per cent (five of 59) and those of controls an attack rate of 7.2 per cent (five of 69).

Food. Of the many food establishments in the area of Hotel A 28 restaurants and bars in the local area were selected for inquiry. No restaurant was found to be significantly associated with illness, nor was purchase of food from street vendors.

Two main American Legion events were associated with the distribution of food: a testimonial dinner and a breakfast. There were no significant differences in attendance between case and control delegates for either event and no difference in the proportion of case and control delegates who ate specific foods at the breakfast. No differences were found between the two groups in preferences for snack foods known to have been served in hospitality rooms during the convention.

Tobacco. In 17 case-control pairs, in case-control survey No. 2, the case delegate smoked cigarettes at the time of the convention and the control delegate did not (Table 4). In five case-control pairs the converse was true. The relative risk of illness associated with smoking was 3.4 and was significantly different from unity (chi-square = 5.5, $P<0.05$, McNemar test). Survey of Philadelphia resident cases indicated that no cigarette brand predominated. The average number of cigarettes smoked was greater for case delegates who smoked than in controls who smoked. Cigar or pipe smoking was not associated with illness.

Table 4. History of Cigarette Smoking among Case and Control Pairs at the American Legion Convention, Philadelphia, July 1976.

CONTROLS	CASES		TOTALS
	Smoker	Nonsmoker	
Smoker	14	5	19
Nonsmoker	17	16	33
Totals	31	21	52

Alcohol. No statistically significant differences between case delegates and controls were found for the average number of alcoholic drinks, including beer, consumed each day during the convention. Nine ill Legionnaires, including five delegates of 90 questioned, indicated that they had had no alcoholic drinks during the convention. No association was found between illness and preference for beer, type of hard liquor, mixer or homemade liquor.

Water. In the Legionnaire census, delegates were asked whether they drank any water or consumed any ice at Hotel A. Forty-five of 69 ill delegates drank water as compared with 469 of 976 well delegate controls, a significant difference at the 0.01 level. The relation holds even when corrected for the number of days delegates spent at the hotel. Fifty-three (62 per cent) of 86 ill Legionnaires queried remembered drinking water at Hotel A. No significant association was found between consumption of ice and illness.

Other. No association was found between illness and contact with birds, mammals or souvenirs. Patients did not complain of insect bites. A hypothesis of airborne spread is difficult to test directly, but it is consistent with the observed association of illness with time spent in the lobby and on the sidewalk in front of the hotel. Several patients with Legionnaires' disease and most with Broad Street pneumonia had only transient exposure in these areas and had no identifiable exposure there other than to air.

DISCUSSION

Between July 22 and August 3, 1976, there was a remarkable incidence of febrile respiratory disease among persons who had attended the American Legion Convention from July 21 to 24. From the age distribution of the Legionnaire group attending the convention and recent mortality statistics from Pennsylvania,[5] it can be estimated that 60 deaths per year, or 1.2 per week, would be expected among the conventioneers. The excess number of deaths (26) that occurred in conventioneers between July 27 and August 16 is further evidence of the occurrence of an epidemic. The outbreak involved, in addition, other visitors to the headquarters hotel and persons who had walked within a block of the hotel, but the outbreak did not appear to be more widely spread in Philadelphia. Clinical, epidemiologic and laboratory results indicated that the large majority of cases that met the criteria for Legionnaires' disease and for Broad Street pneumonia were in fact the same disease.

The shape of the epidemic curve, with its rapid upswing and the incubation period of two to 10 days, suggests a continuing common-source exposure. There is no evidence of spread from person to person. At a minimum, exposure appears to have occurred on July 22 and 23 and also sometime in each of the intervals August 1-3 and August 6-9. Two cases of apparent exposure in Philadelphia only before July 22 were unusual in that their apparent incubation periods were long (16 and 26 days). One could speculate that these patients may have been exposed after leaving Philadelphia, perhaps in their common home town, but there is no direct evidence to confirm that hypothesis. The highest risk of exposure is likely to have been during the time of the American Legion Convention. Whether or not a low-grade exposure was present from July 24 to 31 or after August 9 is unknown, but there is no evidence that the outbreak in the area continued after August, 1976. Serologic survey of the employees of Hotel A suggests the possibility of a low-grade or intermittent exposure to the same or a similar agent for several years.

The place of exposure cannot be defined with certainty, but the most reasonable hypothesis is that exposure occurred within or in the immediate vicinity of Hotel A. Such a hypothesis is consistent with the observation that of delegates, those who stayed at Hotel A had a significantly higher rate of illness than those who did not, and that of the delegates who did not stay at Hotel A, those who fell ill spent more time on the average in Hotel A than those who stayed well.

The fact that cases occurred in persons who had been near, but not in, Hotel A (cases of Broad Street pneumonia) shows that in at least some cases, exposure occurred outside Hotel A, and suggests that exposure could have occurred on the streets or sidewalks around that hotel. Other evidence of exposure outside the hotel comes from the observation that serologically confirmed cases in delegates occurred more frequently in those who watched the parade from the sidewalk in front of Hotel A and that the length of time spent on the sidewalk was associated with illness. Exposure may well have occurred within Hotel A also. In the delegate group, there was a strong association between time spent in the lobby of Hotel A and risk of contracting the disease both for all cases and for those serologically confirmed. Initially, it seemed that the absence of noteworthy illness in employees who worked in the lobby of Hotel A was evidence against the lobby as a site of exposure. However, serologic survey of hotel employees suggests that a large proportion of them may have been immune. Twenty-nine per cent had a titer of 1:64 — a titer that is just below that considered diagnostic of recent infection.[3] The prevalence of this borderline titer in hotel employees is considerably higher than that observed in groups not associated with the outbreak of Legionnaires' disease.[3]

It is unlikely that the place of exposure was in any of the main convention function rooms in Hotel A because attendance at those functions was not associated with illness. Similarly, bedrooms were unlikely places of exposure since roommates of patients were not at increased risk of illness and because there was no geographic clustering of bedrooms of cases in Hotel A. Because no hospitality room was said to have been visited by more than half the patients and because there was no striking association between attendance or food consumption and illness, the rooms are unlikely to have been the sites of exposure.

The mode of spread is not proved, although it was probably air borne. It is clear from the studies of families who did not come to the convention that secondary person-to-person spread was unusual or nonexistent. The possibility that the initial exposure at the convention was by person to person is not ruled out entirely, but the uniform attack rate across districts militates against the possibility. The failure to implicate a common meal at the convention, the street vendors, foods served at the hospitality rooms or any of the local coffee shops or restaurants argues against a food-borne outbreak.

The possibility of a water-borne illness is raised because patients were more likely than controls to state they drank water at Hotel A. However, 35 per cent of ill delegates and 38 per cent of all ill persons queried said that they never drank water at Hotel A. Furthermore, none of those who had Broad Street pneumonia drank water from Hotel A.

The occurrence in the summer would be consistent with spread by an arthropod vector, but bites were not noted by the ill patients.

If the exposure was air borne, the association of illness and time spent in the lobby might be explained. An air-borne agent might also have affected non-Legionnaires who were in the hotel only transiently and had no other apparently noteworthy exposure; it might also have exposed persons who walked near the hotel but did not enter it.

The source of the bacterium is not known, nor is the reason for the sudden appearance of the outbreak in late July and disappearance in mid-August. It does seem that exposure continued for 16 to 19 days, more intensively at first and then trailing off. Efforts are under way to determine if the bacterium can be found in local bird or rodent populations or in dust and dirt. The relatively high proportion of Hotel A employees — especially long-term employees — with indirect fluorescent-antibody titers of $\geqslant$1:64 suggests that exposure to the organism may have been present intermittently for several years. Serologic testing of employees of surrounding businesses is under way to assess the breadth of exposure.

Two previous outbreaks caused by this or a related bacterium also had the pattern of a continuing common-source air-borne exposure.[6,7] In one, an air-conditioning system was instrumental in spreading the agent,[6] but in the other the involved buildings were not air conditioned.[7] In each of those outbreaks, nearby excavation was suspected as an inciting activity. In Philadelphia, however, no nearby excavation in July was identified. All three outbreaks occurred in the summer, but the implications of this apparent seasonality remain speculative.

Sporadic cases of pneumonia caused by this bacterium have been observed.[3] To investigate the clinical characteristics, mode of spread and source of infection of sporadic cases, a case-control study of undiagnosed pneumonia has been organized in Pennsylvania, Ohio, Maryland, Connecticut, Delaware, Florida and the District of Columbia.

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ENVIRONMENTAL MEDICINE

MERCURY IN HOUSE PAINT AS A CAUSE OF ACRODYNIA[*]

Effect of Therapy with N-Acetyl-D,L-Penicillamine

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BOSTON

IN 1948 Warkany and Hubbard[1] indicted mercury ingestion as an etiologic factor in acrodynia. Other reports establishing mercury as the most important cause of acrodynia soon followed.[2-8]

Dimercaprol (BAL), which chelates mercury, was quickly introduced as a therapeutic agent in 1948 but has given variable results.[6,9-15] Edathamil calcium disodium (EDTA) when given for therapy of acrodynia did not significantly increase mercury excretion.[16] Increased urinary elimination of mercury during penicillin therapy for infection has been observed,[17] but the results of penicillin therapy in acrodynia have been equivocal.[17,18]

Aposhian[19,20] has shown that N-acetyl-D,L-penicillamine is more effective than other penicillamine derivatives in protecting laboratory animals from induced inorganic mercury poisoning and that its toxicity is considerably less.[19,20] Smith and Miller[21] reported the successful treatment of mercury poisoning in a gilder with N-acetyl-D,L-penicillamine.

The patient described below was discovered to be excreting mercury in the urine. In this patient the urinary elimination of mercury was greatly enhanced by treatment with N-acetyl-D,L-penicillamine. The mercury was found in a water-base house paint, and we believe this to be the first report of acrodynia from this source of mercury. An organic compound, phenyl mercuric propionate, had been incorporated into the house paint to prevent growth of molds. Both ingestion of the paint and inhalation of its vapor could have resulted in mercury toxicity.

CASE REPORT

E.L. (M.G.H. 1182958), a 5-year-old white boy, was in good health until 3 months before admission, when generalized abdominal pain, which became more intense during or soon after meals, developed. Two months later pruritus of the hands, followed by complaints of pain in his shoulders, arms, legs and knee joints, developed. He had muscular weakness of the lower extremities and occasionally fell to the ground. Two weeks before admission here he entered another hospital with a tentative diagnosis of rheumatic fever. Two determinations of the erythrocyte sedimentation rate were 4 mm. and 5 mm. per hour. The antistreptolysin-O titer and an electrocardiogram were normal. He became irritable and continued to complain of pain in the extremities. He was transferred to another hospital, where the diagnosis of acrodynia was made by Dr. Douglas W. Walker, of Laconia,

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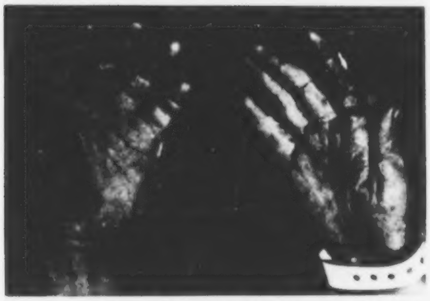

Figure 1. *Typical Changes in the Skin of the Hands. The skin is scaly and has a pink color.*

New Hampshire. A urinary level of 0.09 mg. of mercury per liter, with a urinary specific gravity of 1.004, confirmed the clinical diagnosis. (Normally, no mercury is found in the urine; the hazard level for industrial workers is 0.20 mg. of mercury per liter, with a specific gravity of 1.024.) The patient was referred to the Massachusetts General Hospital for further evaluation and treatment.

Upon admission he had the typical symptoms and signs of acrodynia. These included complaints of pain in the abdomen, extremities and joints, irritability, swinging changes of mood, a marked degree of photophobia, increased perspiration, desquamation and pink color of the hands (Fig. 1), hypertension, hypotonia, salaam positioning (Fig. 2), anorexia and insomnia. His weight was 17 kg., and the body-surface area 0.7 square meter.

Laboratory studies included a normal hemogram and normal electrolytes, blood urea nitrogen, albumin, globulin, serum glutamic oxalacetic transaminase and alkaline phosphatase. An L. E.-cell preparation was negative.

Lumbar puncture revealed a normal spinal-fluid pressure, protein, sugar and colloidal-gold curve. An electroencephalogram was interpreted as being a moderately abnormal waking record because of asymmetry of the 2 sides. There was poor driving and response to strobe on the left. A repeat electroencephalogram 3 days later revealed no marked change.

X-ray films of the skull, knees, shoulders and an intravenous urogram* were normal. X-ray study of the teeth revealed extensive caries involving the deciduous teeth, and several permanent teeth were loose.

Urinalysis was within normal limits. The urine contained trace amounts of lead, but no protein or arsenic. The creatinine clearances were 53 and 54 liters per day. The 24-hour urinary coproporphyrin excretion was normal. Catechol amine studies, done because of clinical signs of increased sympathetic activity, showed a urinary excretion of 3 microgm. of epinephrine and 79 microgm. of norepinephrine per 24 hours. The vanilmandelic acid excretion was 3.5 mg. per 24 hours.

Figure 2. *Typical Posture Assumed by the Patient. He is burrowing his head into the pillow to blot out the light.*

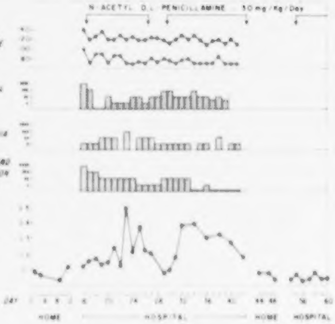

Figure 3. *Response to N-acetyl-D,L-penicillamine (0 = Normal, + = Slightly Abnormal, + + = Mildly Abnormal, + + + = Moderately Abnormal, and + + + + = Severely Abnormal, as Seen in Acrodynia).*

Aliquots of twenty-four-hour urine collections were used for the mercury determinations. The average twenty-four-hour volume range was 500 to 800 ml.

Urine specimens were quantitatively analyzed for mercury throughout the course of the patient's illness with the use of a modification of the Monkmon method.[22] Samples of urine were cold digested with potassium permanganate and sulfuric acid to destroy the organic material. The excess potassium permanganate was bleached with hydroxylamine hydrochloride, and after adjustment to a pH of 6, the solution of the soluble divalent mercury was passed through a glass filter impregnated with cadmium sulfide. The mercury in solution was retained on the pad as a sulfide. The sulfide was then placed in a flask and heated. Evolved mercury was drawn through a General Electric Mercury Vapor Detector, and the readings plotted at 10-second intervals. Standard urines containing known amounts of mercury were treated in a similar manner, and the readings compared with that of the unknown solutions. (The method is very sensitive and is reproducible to less than 0.1 microgm. of mercury per aliquot.)

The patient was treated with N-acetyl-D,L-penicillamine,* 0.125 gm. given 4 times a day (30 mg. per kilogram of body weight per day). The urinary excretion of mercury is shown in Figure 3. The mercury levels of the urine samples rose with treatment, diminished upon discontinuation and were again elevated with the reinstitution of treatment. The daily clinical course, emphasizing change in blood pressure, frequency of abnormal posturing, photophobia and redness and desquamation of the hands, is charted in Figure 3. There was some increase of pain, a slight increase of erythema of the palms, more frequent salaam posturing and greater fluctuation of mood when therapy was discontinued.

With N-acetyl-D,L-penicillamine therapy the patient showed general improvement except for his behavior. This became progressively worse as evidenced by refusal to eat, lying on the floor, throwing away urine specimens and great fluctuation in mood. However, when he was informed of his impending discharge, his behavior became much improved. A follow-up electroencephalogram had reverted to normal.

At home his behavior again became a problem, necessitating readmission 11 days after discharge. He was given a 6-day course of N-acetyl-D,L-penicillamine. His behavior markedly improved although there was no significant increase in the urinary mercury excretion. After 8 days in the hospital he was discharged, and since this last discharge he has maintained his clinical improvement. Ten months later a urine sample contained 0.016 mg. of mercury per liter.

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*Obtained from Dr. Alfred Bader, Aldrich Chemical Company, Milwaukee, Wisconsin.

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In an attempt to discover how this child was exposed to mercury, the patient's home was examined by the New Hampshire Department of Public Health, but no source was found. It was then learned that the patient had helped his mother paint part of the kitchen and bedroom 4 months before the onset of symptoms. There was no definite history of ingestion of paint although this remains a possibility. The paint used was analyzed and found to contain mercury by the method already described for the urine samples. The sleeping quarters were very small. The parents, a 3-year-old brother and the patient all slept in the same room, whose dimensions were 10 by 10 by 8 cubic feet. Other members of the family whose urine was sampled for mercury had none in a single sample. They had no signs of mercury intoxication.

The concentration of metallic mercury in the paint was found to be 0.02 per cent on a weight basis, or 0.036 per cent phenyl mercuric propionate. To determine the rate of evaporation of mercury from the paint and whether the mercury concentration of the surrounding air could reach appreciable levels, a panel 8 by 2⅝ inches was painted with an average coat of paint on a painted surface of 37 square inches. The panel was suspended in a 1.9-liter enclosed jar. Air was passed through the jar at a rate of 1 liter per minute, and periodic measurements of the mercury concentration in the jar were made with the General Electric Mercury Vapor Detector. The amount of vapor from the freshly painted panel in equilibrium with air at a flow rate of 1 liter per minute was 0.17 mg. of mercury per cubic meter of air at the end of the 1st 30 minutes, for a calculated average volatilization rate of 0.50 microgm. of mercury per minute per square foot. The test panel continued to emit mercury vapor in diminishing amounts for 6 weeks despite continuous air exchanges. On the basis of an average volatilization rate of 0.50 microgm. of mercury per minute per square foot, it was calculated that a room 10 by 10 by 8 cubic feet in which the 4 walls had been painted with an average coat of this mercury-containing paint and ventilated at the rate of 2 air exchanges per hour would have an average concentration of 0.21 mg. of mercury per cubic meter of enclosed air. The concentration in the surrounding air considered acceptable for continuous adult exposure without toxic effect is 0.10 mg. of mercury per cubic meter.*

DISCUSSION

The amount of mercury considered of etiologic importance in acrodynia may be small, and the interval between the exposure to mercury and the onset of the disease in the reported cases varies from one week to several months. That the patient was the only member of his family clinically affected by the mercury may be explained by his greater exposure during the painting of the rooms, by the possibility of ingestion of the paint or by an idiosyncrasy to mercury. It was not possible to quantitate the amount of mercury absorbed by the patient.

The improvement after the initiation of N-acetyl-D,L-penicillamine therapy may have been fortuitous. Normally, the course of untreated cases lasts from months to a year. Since mercury seems to be the offender in acrodynia its more prompt elimination from the body should be beneficial. The marked spontaneous variation in the daily elimination of mercury[23] makes it difficult to evaluate precisely the effects of drugs on its excretion. Furthermore, the marked individual susceptibility to mercury may lead to considerable variation in clinical course quite apart from the use of chelating compounds. Perhaps some people require a much greater reduction of the body pool of mercury before cessation of symptoms. Whether acrodynia represents an allergic reaction to mercury, as originally suggested by Helmick,[24] or is merely an expression of individual idiosyncrasy to the toxic effects of the metal has been amply discussed by Warkany and Hubbard,[25] who favor the latter hypothesis.

N-acetyl-D,L-penicillamine is the acetylated congener of D,L-penicillamine. Unlike D,L-penicillamine, it will not increase urinary excretion of copper.[20] It appears that N-acetyl-D,L-penicillamine is a more effective sulfhydryl donor.

The course with N-acetyl-D,L-penicillamine in the case reported above compares favorably with that in cases treated with BAL.[6,9-10] Although N-acetyl-D,L-penicillamine has not had as extensive a clinical trial as BAL, there is no evidence that it shares the known toxicity of BAL and, unlike that compound, it is administered orally. It has been shown to be less toxic than D,L-penicillamine in experiments in rats.[19,20] The patient described above gave no sign of sensitivity to the drug such as rash, fever, leukopenia or thrombocytopenia. The six-day course of therapy during the last admission was marked by a vast clinical improvement although the urinary excretion of mercury did not increase. Presumably, the labile body stores of mercury had been depleted by the previous course of therapy. In the treated case of mercury poisoning reported by Smith and Miller[21] clinical improvement with N-acetyl-D,L-penicillamine therapy could not be correlated with mercury excretion, and they suggested that the amount of mercury excreted may be much less important than the amount complexed in an inactive form in blood and tissues.

It is interesting that the twenty-four-hour urinary catechol amine excretion in the present case was elevated. Feer,[26] in 1925, attributed acrodynia to a disorder of the vegetative nervous system and used atropine to treat his cases. Stolz[27] reported hyperplasia of the chromaffin system in acrodynia. Blackfan and McKhann,[28] after studying 40 cases, observed that sympathetic overactivity accounted for most of the symptoms; they found that the pulse rate of patients with acrodynia did not vary during sleep as in normal subjects. Day et al.[29] concluded that emotional stresses failed to elicit normal vegetative responses from patients with acrodynia. They thought that this might be explained by pre-existing maximum stimulation of the sympathetic nervous system and compared acrodynia to pheochromocytoma. Hubble[30] stressed the similarity between acrodynia and pheochromocytoma. Excessive vasoconstriction was found by Vulliamy[31] in 10 of 11 cases of acrodynia. Reflex vasodilatation of the hands, which normally follows heating of the trunk and legs, was absent. This capacity was regained with the use of tolazoline hydrochloride (Priscoline) and tetraethylammonium bromide. Farquhar et al.[32] described increased urinary sympathin in 3 of 4 cases of acrodynia as compared with normal children. Cheek and his associates[33,34] demonstrated that calomel potentiates the effect of epinephrine in the rat, and suggested that mercury potentiates sympathetic activity in acrodynia. Peterson and Laughmiller[35] reported the relief of symptoms in 6 of 7 cases of acrodynia treated with tolazoline. Bower[36] noted relief of all symptoms except for photophobia with sympatholytic drugs such as hexamethonium tartrate and pentolinium bromide; he confirmed the relief of arteriolar spasm in patients with acrodynia by these drugs. Ritzel, Berger and Roulet[37] recently observed increased catechol amine excretion in a case of acrodynia. Now that better methods for the determinaton of urinary catechol amines are available, sympathetic activity in acrodynia should offer a field for fruitful investigation.

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*Threshold-limit values for 1962, adopted at the twenty-fourth annual meeting of the American Conference of Governmental Industrial Hygienists, Washington, D.C., May 13-15, 1962 (reprints may be obtained from the Secretary Treasurer of the American Conference of Industrial Hygienists, 1014 Broadway, Cincinnati, Ohio).

Another interesting and unique finding in this case is the apparent source of mercury in the house paint. The demonstration that potentially harmful levels of mercury could result from vaporization of these paints supports this conclusion. The patient's home, household contents and surrounding areas were examined by both the New Hampshire Department of Health and ourselves. The only source of mercury that could be detected was found in the paint. The amount of mercury in the urine and the length of time during which it was excreted implies that the inhalation of mercury vapor by the patient occurred over a long period. The discovery of mercury in the paint and our studies of the continuing emission of mercury into the air surrounding the painted surfaces present a new and potentially common cause for mercury poisoning. One wonders if there may be patients with some of the more subtle signs and symptoms of acrodynia in whom this diagnosis is not being considered. The paint manufacturer's responsibility is a matter of public-health interest. Mercury-containing paint should be labeled properly and should indicate the possible danger to children upon ingestion or exposure to the toxic vapors. These mercury-containing paints should be limited to outdoor use.

Summary and Conclusions

A case of acrodynia in a patient who had increased urinary excretion of mercury is presented. New methods for mercury analysis are described. The source of mercury was found in house paint, and the epidemiologic implications of this finding are discussed.

The patient was treated with N-acetyl-D,L-penicillamine, which markedly increased the urinary output of mercury.

The rationale for this form of therapy in acrodynia is presented and compared with previously reported therapeutic methods.

Increased excretion of catechol amines was found in the urine. The relation of this finding to theories of the pathogenesis of acrodynia is considered.

We are indebted to Dr. Douglas W. Walker of Laconia, New Hampshire, for referring this patient to our service and for assistance in the collection of essential data, to Drs. Harriet L. Hardy and John D. Crawford, of the Massachusetts General Hospital, for inspiration and guidance, to the New Hampshire State Department of Health for help and interest, to Mr. Frederick Viles, Jr., and Mr. Richard Chamberlin, of Massachusetts Institute of Technology, for aid in the mercury determinations and to Dr. Nathan B. Talbot, chief of the Children's Service, Massachusetts General Hospital, for guidance and helpful suggestions in the preparation of the manuscript.

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ATSDR March 1992

Case Studies in Environmental Medicine

17

Mercury Toxicity

Environmental ALERT . . .

☑ ***Some latex house paints release dangerous levels of mercury vapor. Check the label. Latex paints sold after August 1990 must carry a warning if they contain a mercury additive.***

☑ ***A recent study by the National Institutes of Health indicates that the small amounts of mercury released in the mouth by dental amalgams pose no known danger to health.***

☑ ***Because mercury has several forms and produces subtle effects at chronic low-level exposures, mercury toxicity can be a difficult diagnosis to establish.***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. See page 23 for further information about continuing medical education credits and continuing education units.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

A 3-year-old boy with irritability, digital erythema, and leg pain

A 3-year-old boy is brought to your office by his parents, who state that the child refuses to play and prefers to lie on his bed. His parents note that about a month ago, he seemed to withdraw and become cranky. Recently, he has experienced night sweats. On those nights the child has felt warm, but his parents did not take his temperature. The child has had no other symptoms, such as a runny nose or cough, and has not lost weight.

History reveals that the patient had recurring ear infections this past winter, which were treated with oral antibiotics. His growth and development have been normal; he is in the 90th percentile for weight and height. The child's immunizations are up to date, and he is on no medications.

During physical examination, the boy is uncooperative and crying. He refuses to walk or stand and says that his legs "hurt." He is afebrile, has a heart rate of 130 per minute and respirations of 16 per minute. He is sweating, and his nose, fingers, and toes are erythematous; the skin on his fingers and toes is peeling. The oral pharynx and abdomen appear normal upon examination; his lungs are clear. He does not have point tenderness in his legs, and he has full range of motion in knees and hips. His ankles are not edematous. Results of the neurologic examination are normal; there is no muscular atrophy. Other findings are unremarkable.

Three months ago, the child, his parents, and his 6-year-old sister moved into a freshly painted house. The parents report that their daughter appears healthy and is doing well in first grade. Both parents are school teachers in good health. The family has no pets and has not traveled within the past year. Until recently, the boy has enjoyed most social activities with his family.

Pretest

(a) What should be included on the patient's problem list?

(b) What is the differential diagnosis for this patient?

(c) What tests would you recommend to confirm or rule out a diagnosis?

(d) What treatment and follow-up would you recommend?

Answers can be found on pages 21-2.

Exposure Pathways

☐ **Elemental mercury vapor accounts for most occupational and many accidental exposures.**

☐ **The major source of organic methylmercury exposure in the general population is fish consumption.**

☐ **Mercury-containing dental amalgams have not been proven to cause adverse health effects.**

Mercury (Hg) is a metal found in the environment in its elemental state and as organic and inorganic compounds. For 3000 years, mercury, in various forms, has been used in medicine and industry. Although most medicinal uses have been discontinued, industrial uses of mercury are increasing.

Mercury exists in three forms: elemental mercury (Hg^0), inorganic mercury salts (Hg^{1+} and Hg^{2+}), and organic mercury. Elemental mercury is a silver-gray liquid at room temperature that vaporizes readily when heated. Commonly referred to as quicksilver or metallic mercury, it is used in thermometers, thermostats, switches, barometers, batteries, and other products. Elemental mercury vapor accounts for most occupational exposures.

The intermediate oxidation state, Hg^{1+}, forms numerous mercurous salts; the best known is mercurous chloride or calomel, which was commonly used in teething powders and other medicines until its adverse effects were publicized in 1948. The highest valence state, Hg^{2+}, forms a variety of mercuric salts, which are used to inhibit bacterial or fungal growth. Most mercurous and mercuric salts readily disassociate into ions in the body.

Under appropriate conditions, Hg^{2+} can covalently bind carbon to form organomercury compounds; the most important in terms of human exposure is methylmercury (MeHg). MeHg is the form most frequently involved in mercury food poisoning. Elemental mercury and MeHg compounds have a greater ability to cross cell membranes than do the mercurous or mercuric salts and are consequently more neurotoxic than mercury salts.

The major source of atmospheric mercury is the global off-gassing of mercury from soils and surface waters. Burning of fossil fuels, particularly coal, contributes to the level of mercury in the atmosphere. The airborne level is increased by disposal of solid waste (e.g., thermometers, electrical switches, and batteries) in landfills; application of mercury-containing paints, fungicides, and pesticides; and combustion of waste oils.

Weathering of mercury-bearing rock and industrial effluents are the major sources of mercury contamination in water. Elevated mercury concentrations have been detected in approximately 25% of the groundwater and surface-water samples from 2783 hazardous waste sites tested by the Environmental Protection Agency (EPA). Groundwater surveys also have detected elevated mercury concentrations in some drinking-water supplies. Industrial processes that may produce mercury-containing effluents include chlorine and caustic soda production, mining and ore processing, metallurgy and electroplating, chemical manufacturing, ink manufacturing, paper milling, leather tanning, textile manufacturing, and pharmaceutical production.

Any mercury compound released into the environment becomes available for potential methylation to MeHg by microorganisms indigenous to soils and waters. Higher methylating rates are associated with acidified waters. MeHg in surface waters rapidly accumulates in fish and other aquatic organisms. The mercury concentration in fish at the top of the food chain is typically biomagnified up to 100,000 times the concentration in surrounding waters.

In the general population, diet is the major source of mercury exposure, primarily through fish consumption. Predacious fish (e.g., pike in freshwater, tuna and swordfish in marine water) can have more than 50 times the average mercury concentration found in most other fish. Between 70% and 90% of the total mercury detected in fish is in the form of MeHg. The U.S. Food and Drug Administration (FDA) is responsible for regulating commercial fish. Regulations require that marketed fish contain no more than 1 part per million (ppm) of mercury. Many states have lower advisory levels for sport fish. Other potential sources of dietary exposure are the consumption of fish-eating birds and mammals and consumption of game birds in areas where mercury-containing pesticides have been used. During the winter of 1971-72, thousands of Iraqis were poisoned by consuming homemade bread prepared from seed wheat that had been treated with a MeHg fungicide.

According to EPA, approximately 30% of interior latex paint manufactured before 1990 contained mercury compounds to prevent bacterial and fungal growth. In 1989, a case of acrodynia (a rare disease in children caused by mercury; see page 13) in a 4-year-old boy occurred 10 days after the child's home was painted with a mercury-containing interior latex paint and was not ventilated. Mercury-containing paint can raise the total indoor air mercury concentration by 1000 times the level before painting. Paint manufacturers agreed to stop using mercury in interior paint after August 20, 1990; however, sale of existing stocks of interior latex paints was allowed until July 1991. Paint manufacturers also have agreed to place labels on mercury-containing exterior paint with a warning that the paint is for outdoor use only. Mercury use in exterior paint was discontinued after September 1991. Mercury-containing joint compound, plasters, and adhesives must be labeled appropriately; sale to distributors was allowed until June 1991. Because many people keep partly used cans of paint for repainting, pre-1990 paints may continue to be a source of mercury exposure for years.

Medical treatments and some cosmetics constitute another source of potential mercury exposure. Mercurials have been used for hundreds of years for a variety of therapeutic purposes including cathartic, diuretic, antisyphilitic, antiseptic, antipruritic, anti-inflammatory, antiparasitic, and vermifuge. Metallic mercury has been used by Mexican-American and Asian populations in folk remedies for chronic stomach disorders and by Latin-American and Caribbean natives in occult practices. Mercurials are still used as preservatives in some eye drops, eye ointments, nasal sprays, vaccines, and as antiseptics and diuretics. Gammaglobulin preparations contain Merthiolate™*, a mercury-containing biocide. Elemental mercury in a Miller-Abbott tube, which is used for intestinal decompression, provides the weight that assists the tube in traversing the GI tract.

Silver dental amalgams, which have been used for the past 150 years to fill cavities in teeth, can be 50% elemental mercury by weight. About 200 million mercury restorations are performed in the United States each year; at least one-half of those use silver amalgam. The mechanical action of chewing on an occlusive filling releases trace quantities of mercury vapor, which are partially absorbed. Typically, exposure to mercury from amalgams is less than exposure from foods such as tuna or swordfish that contain MeHg, a more toxic form of mercury. It is estimated that people with many amalgam fillings receive less than 1% of the daily mercury vapor dose that is considered occupationally safe. A National Institutes of Health expert panel recently concluded that amalgam fillings pose no significant risk of side effects and should not be replaced simply because they contain mercury.

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* Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

Challenge

(1) What are the possible exposure sources of mercury for the patient in the case study?

Who's at Risk

A 1980 survey by the National Institute for Occupational Safety and Health (NIOSH) estimated that 70,000 workers, of whom about one-third were women, were potentially exposed to mercury (primarily mercury vapor) in the workplace. Most of these workers were employed as laboratory technicians, registered nurses, and machine operators. Household members of occupationally exposed workers may also be at increased exposure risk because mercury can be brought into the home on contaminated clothes.

Personnel potentially exposed to mercury include, but are not limited to, the following:

chlorine and caustic soda production workers

cosmetic producers

dental personnel

electroplators

explosives manufacturers

felt makers and leather tanners

grinding machine operators

hazardous waste site personnel

ink manufacturers

laboratory personnel

manufacturers of batteries, fluorescent lamps, mercury vapor lamps, switches, rectifiers

metallurgists

miners and processors of cinnabar (HgS), gold, silver, copper, zinc

paint and pigment manufacturers

painters

paper millers

pesticide/fungicide production and application workers

pharmaceutical producers

plumbers

Fetuses, infants, and children are at increased risk of adverse effects of MeHg. MeHg readily crosses the placenta during the prenatal stage, when the nervous system is most sensitive to mercury poisoning. Because MeHg concentrates in breast milk, nursing infants can be affected.

Children are attracted to the appearance and unique properties of liquid elemental mercury and are at risk of ingesting elemental mercury, as well as mercury-containing dust and soil, because of natural mouthing behaviors. Infants and children are at increased risk of inhaling elemental mercury because mercury vapor is heavier than air and tends to settle to the floor.

- ☐ **Workers using mercury or mercury-containing products, as well as their household members, may be at increased risk of exposure to mercury vapor.**
- ☐ **Fetuses, infants, and children are at greatest risk of MeHg's adverse effects.**
- ☐ **Children are at increased risk of exposure to elemental mercury vapor in the home because mercury vapor tends to settle to the floor.**

Because many people are increasing their consumption of fish in an effort to lower blood cholesterol concentrations, mercury exposure through diet may be increasing. Mercury is a contaminant of many fresh and marine waters. In the 1950s, hundreds of people were mercury-poisoned in Japan after consuming fish from Minamata Bay. The incident caused 41 deaths and at least 30 cases of infantile cerebral palsy. The source of contamination was effluent discharged into the bay from a factory using a mercury catalyst to make vinyl chloride.

Neurologic and behavioral disorders have been observed in persons after ingestion or dermal application of inorganic mercury-containing compounds in teething powders, skin-lightening ointments, and laxatives. Most of these products have been withdrawn from the market or are no longer available in the United States. Yellow mercuric oxide reportedly caused acrodynia (see Signs and Symptoms) in a 4-month-old boy being treated for eczema. Long-term abuse of a mercury-containing laxative was the cause of death in at least one patient.

Challenge

(2) Besides the patient, who else in the case study may be at risk of mercury exposure?

Biologic Fate

Elemental Mercury

Mercury's absorption and metabolism depend on its chemical and physical form. Inhaled as a vapor, elemental mercury is almost completely absorbed (about 80%) and diffuses rapidly across the placental and blood-brain barriers (Table 1). At the cellular level, dissolved vapor is oxidized to Hg^{2+}. Ethanol, even at nonintoxicating levels, inhibits mercury oxidation in the blood and prolongs elemental mercury's half-life in the body.

☐ **The chemical and physical form of mercury determine its absorption, metabolism, distribution, and excretion pathways.**

When ingested, elemental mercury is poorly absorbed from the gastrointestinal tract (about 0.01%). The surface of the metal probably becomes coated rapidly with endogenous sulfur-laden compounds, which impairs diffusion across the gastrointestinal mucosa. A 17-year-old boy reportedly ingested 204 grams (g) of elemental mercury without systemic toxicity. Animal studies indicate that elemental mercury as a liquid or vapor can be absorbed percutaneously.

☐ **Elemental mercury is almost completely absorbed when inhaled, but poorly absorbed when ingested. It readily crosses the blood-brain barrier.**

Table 1. Clinical importance of various forms of mercury

Form	State	Source	Absorption*	Primary Effects	Secondary Effects
Inorganic Elemental					
Liquid Hg†	Hg^0	Thermometers, barometers	Dermal contact: minimal absorption Ingestion: poor absorption	§	
Mercury Vapor†	Hg^0	Industrial	Inhalation: 80% absorbed Percutaneous: minimal absorption	Lungs, skin, eyes, gingiva	CNS¶, kidneys
Salts					
Mercurous	Hg^{1+}	Medicines, antiseptics	Ingestion: ~10% absorbed Dermal contact: lethal doses can be absorbed by animals	Kidneys, GI tract¶	CNS
Mercuric	Hg^{2+}				
Organic					
Methylmercury†	CH_3Hg-	Fish	Ingestion: 100% absorbed Inhalation: absorbed readily	CNS	
Phenylmercury	C_6H_5Hg-	Fungicides, bactericides	Ingestion: 80%-100% absorbed Dermal contact: See Salts above	Kidneys	CNS

[*] In humans, the biologic half-life of all forms of mercury is 40 to 70 days

[†] Crosses the blood-brain barrier

[§] Liquid elemental mercury is poorly absorbed through the intestinal tract (0.01%) or dermally; systemic toxicity is rare.

[¶] CNS = central nervous system, GI tract = gastrointestinal tract

The urine and fecal elimination pathways account for most of the excretion of elemental mercury. Exhalation of mercury vapor and secretion of mercuric ions in saliva and sweat contribute to the elimination process. The biologic half-life of inhaled elemental mercury in humans is approximately 60 days.

Mercury salts

- ☐ **Mercuric salts are generally more toxic than mercurous salts.**
- ☐ **Mercury salts do not cross the blood-brain barrier as readily as elemental mercury does.**

On average, less than 10% of an ingested mercury salt is absorbed from the gastrointestinal tract. Dermal absorption of ionic mercury salts also can cause toxicity. In general, mercuric (Hg^{2+}) salts are more soluble and produce more serious poisonings than mercurous (Hg^{1+}) salts. Mercuric salts are usually colorless or white crystals or intensely colored yellow or red powders; they include mercuric chloride (antiseptic and disinfectant), mercuric cyanide and mercuric oxide (topical antiseptics), and mercuric nitrate (used in working with felt). Mercurous salts are typically colorless, white, or light yellow powders; they include mercurous acetate (antibacterial agent), mercurous chloride or calomel (cathartic, diuretic, antiseptic, and antisyphilitic agent), mercurous nitrate (used to blacken brass), and mercurous oxide (used to make electric batteries).

The tissue distribution and excretion pathways of mercury salts are similar to those of mercury vapor; however, mercuric and mercurous ions cross the blood-brain and placental barriers to a much lesser extent than inhaled elemental mercury. In humans, mercury salts have a shorter biologic half-life (about 40 days) than inhaled elemental mercury.

Organic mercury

- ☐ **Organomercurials are absorbed well regardless of exposure route.**
- ☐ **MeHg concentrates mostly in the blood and brain.**

Organomercury compounds are readily absorbed by inhalation, dermal contact, and ingestion. MeHg is distributed uniformly to all tissues, although it concentrates more in the blood and brain than elemental mercury or mercury ions do. About 90% of MeHg is found in the red blood cells, where it is metabolized to mercury ions at a slow rate. The major route of MeHg excretion (about 90%) is through bile into the feces; urinary excretion accounts for most of the remaining 10%. The biologic half-life of MeHg is about 70 days in humans.

Although considered organomercurials, phenylmercury compounds are absorbed less efficiently by the gastrointestinal system than MeHg compounds. Because phenylmercury is rapidly metabolized in the body to Hg^{2+}, its effects are similar to those of mercury salts. Metabolites of phenylmercury are excreted mainly in the urine.

Physiologic Effects

Effects of mercury toxicity manifest primarily in the central nervous system (CNS) and kidneys, where mercury accumulates after exposure. The duration, intensity, and route of exposure, and the form of mercury influence which systems are affected. The primary organ system affected by chronic exposure to elemental mercury and organomercury compounds is the nervous system; the primary organs affected by chronic exposure to mercury salts are the kidneys. In acute poisonings, the respiratory system is affected by inhaled elemental mercury and the gastrointestinal system by ingested mercury salts. The cardiovascular system may be affected secondarily.

- ☐ **The central nervous system and kidneys are key targets of mercury toxicity.**
- ☐ **In acute poisonings, the respiratory and gastrointestinal systems can be affected.**

The precise mechanism of action for all forms of mercury is unclear. Mercury ions (Hg^{1+} and Hg^{2+}) alter the structure and function of enzymes and other proteins by binding to sulfhydryl groups. Mercury may also interfere with cellular metabolism by binding to amine and phosphoryl groups. MeHg and high levels of inhaled elemental mercury are able to cross the blood-brain and placental barriers. In humans, MeHg exposure has resulted in pronounced adverse neurologic effects in the fetus. The effects of elemental mercury on the human fetus have not been studied thoroughly.

Neurologic Effects

CNS effects result primarily from exposure to elemental mercury vapor and to MeHg. These forms of mercury cross the blood-brain barrier readily and can produce irreversible brain damage. MeHg ingestion leads to delayed CNS symptoms that may not manifest until months after the initial exposure, and early symptoms are often nonspecific, such as malaise, blurred vision, or hearing loss. The peripheral nervous system also may be affected. Some investigators suggest that alteration in neurotransmission may be one mechanism of action for mercury-induced neurotoxicity.

- ☐ **MeHg and inhaled elemental mercury accumulate rapidly in the CNS.**

Renal Effects

After inorganic salts or phenylmercury compounds are ingested, a large amount of mercury may accumulate in the kidneys, producing a generalized increase in the permeability of the tubular epithelium. Exposure to mercury vapor or to mercury salts produces an apparently dose-dependent proteinuria or nephrotic syndrome. Acute tubular necrosis with resultant renal failure may occur.

- ☐ **Severe renal damage can result from ingestion and absorption of mercury salts.**

Developmental Effects

☐ **Evidence indicates that MeHg causes developmental effects.**

☐ **Data are limited on the fetal effects caused by forms of mercury other than MeHg.**

Studies of MeHg concentrations in the blood of newborn infants show a significant correlation with maternal blood levels. In MeHg poisonings, damage to the fetal nervous system is widespread and probably involves derangement of developmental processes such as neuronal migration and neuronal cell division. MeHg also may have a high affinity for fetal hemoglobin. Infants born to women who had ingested flour made from grain treated with a MeHg fungicide had brain damage manifested by mental retardation, ataxia, deafness, constriction of the visual fields, blindness, microcephaly, cerebral palsy, and disturbances in swallowing. In experimental animals, exposure to elemental mercury vapor or administration of mercury salts has produced developmental anomalies, but the relevance of these findings to humans is unknown.

Other Effects

☐ **Severe tissue damage to the lungs (through inhalation exposure) and GI tract (through ingestion exposure) has been reported.**

Respiratory and gastrointestinal effects can occur in acute mercury poisonings. Inhalation of elemental mercury has caused severe pulmonary tissue damage; autopsy has revealed dilation of the right ventricle due to respiratory failure in children who died from mercury vapor inhalation. Gastritis and necrotizing ulceration of the intestinal mucosa can result from ingestion of inorganic salts. Liver damage also has been reported in cases of poisoning due to mercury salts. Both increased and decreased blood pressure have been associated with elemental mercury exposure.

Chromosomal aberrations have been found in some persons working with mercury. There is insufficient evidence to associate mercury with cancer in humans.

Challenge

(3) Additional information for the case study: The patient's mother is 2 months pregnant. Is the fetus at risk of mercury exposure?

Clinical Evaluation

History and Physical Examination

A complete history of a patient with possible mercury toxicity should contain the following information:

- occupation and hobbies of all home occupants.
- recent application of mercury-containing caulks, latex paint, and other materials in constructing or renovating homes and other buildings.
- recent move. Previous tenants may have spilled mercury, or the new home recently may have been painted with mercury-containing paint.
- use of folk medicines. Mercury compounds have been detected in folk and nontraditional healing medications.
- use of cosmetics. Mercury is contained in some mascaras and wave fixatives, and some skin lighteners sold outside the United States.
- use of over-the-counter preparations such as nasal sprays, contact lens solutions, and topical antiseptics.
- source and amount of fish consumed per week.
- use of elemental mercury in a school laboratory.
- playing with mercury. Children are attracted to liquid elemental mercury because of its unique properties.

☐ **A complete history and careful evaluation of the nervous system and kidneys are essential in diagnosing mercury toxicity.**

The nervous system and kidneys should be carefully examined. Recent behavioral changes, such as an increase in irritability or shyness and changes in short-term memory, should be documented. In children, developmental milestones should be evaluated. Blood pressure and liver function also should be assessed. If mercury salts have been ingested and corrosive injury is suspected, endoscopic examination should be performed. If elemental mercury vapor has been inhaled, a chest X ray should be obtained.

Signs and Symptoms

Acute Exposure

Elemental Mercury

Inhalation of elemental mercury vapor may rapidly produce cough, dyspnea, chest pain, nausea, vomiting, diarrhea, fever, and a metallic taste in the mouth. Stomatitis, colitis, nephrotic syndrome, and salivation may occur. Later, interstitial pneumonitis, necrotizing bronchiolitis, and pulmonary edema may develop. According to one case report, a person experienced symptoms characteristic of amyotrophic lateral sclerosis after an intense elemental mercury vapor exposure; symptoms abated as the body burden of mercury decreased. Children less than 30 months of age appear to be at increased risk for pulmonary toxicity, and death may rapidly result

☐ **Pulmonary and CNS effects result from inhaling elemental mercury.**

due to pulmonary dysfunction. Conjunctivitis and an erythematous, pruritic rash have been reported with relatively mild exposures to mercury vapor. Ingested liquid elemental mercury is not absorbed well and therefore poses only limited risk of toxicity. Contact with liquid mercury has been associated with a dermatitis characterized by a papular erythema.

Mercury Salts

- ☐ **The GI tract and, later, the kidneys are affected by ingestion of mercury salts.**

The acute lethal dose of most mercury salts is approximately 1 to 4 g for adults. Symptoms and signs a few hours after ingestion include a metallic taste in the mouth; nausea, vomiting, and bloody diarrhea; severe abdominal pain; tenesmus; intestinal wall necrosis leading to scarring, fibrosis, and possible stenosis; hematemesis; and cardiovascular collapse due to dehydration. The urine may contain protein, casts, and red blood cells. One day to two weeks after ingestion, urine output may diminish due to acute tubular necrosis. Death due to uremia may result.

Organic Mercury

- ☐ **Symptoms due to MeHg ingestion typically are nonspecific and delayed.**

The neurologic effects of MeHg ingestion have been well documented after outbreaks of poisoning in Minamata, Japan, (where fish containing MeHg was consumed) and in Iraq (where grain treated with a MeHg fungicide was consumed). In adults, the earliest signs and symptoms are nonspecific and can take months to develop. These include ataxia; paresthesias; malaise; blurred vision; and impaired hearing, taste, and smell. In Japan, the neurologic effects of MeHg were first observed in cats who ate the mercury-contaminated fish, leading to the colloquialism "cat dancing disease."

The signs and symptoms of poisoning due to aryl organomercury compounds (e.g., phenylmercuric acetate) are similar to those of mercury salts.

Chronic Exposure

Elemental Mercury

- ☐ **Tremor and personality disturbances are characteristic signs of chronic exposure to elemental mercury vapor.**

The most important effects of chronic exposure to elemental mercury vapor involve the nervous system. At chronic low doses, the body oxidizes most of the elemental mercury to mercuric ions (Hg^{2+}), which do not readily cross the blood-brain barrier. At high doses, the body is not able to metabolize the mercury rapidly enough and more elemental mercury reaches the brain. CNS signs and symptoms include psychological changes, insomnia, loss of appetite with weight loss, erethism (characterized by insomnia, excessive shyness, and emotional instability), irritability, headache, and short-term memory loss.

Tremor, though seldom the first sign to appear, is characteristic of exposure; it usually disappears if exposure is stopped. Other peripheral nervous system findings include distal paresthesias, motor and sensory nerve conduction delay, and limb weakness.

Acrodynia, a rare syndrome characterized by severe leg cramps; irritability; paresthesias; and painful pink fingers and peeling hands, feet, and nose, may develop in children exposed to elemental mercury, mercury salts, or phenylmercury (which is rapidly metabolized to Hg^{2+}). It is not known why children but not adults are affected by acrodynia. It is also an enigma why few children exposed to mercury develop acrodynia. If one case is diagnosed, it is likely that other persons have been exposed.

Mercury Salts

According to two case reports, the chronic ingestion of mercury salts in the form of a laxative resulted in irritability, colitis, and chronic renal failure. Gingivitis, stomatitis, and salivation also can occur.

Organic Mercury

The signs and symptoms of chronic exposure to MeHg include a tingling sensation in the extremities; tunnel vision; impaired hearing, taste, and smell; incoordination; tremor; irritability; memory loss; depression; and insomnia. As with acute MeHg exposure, the effects of chronic exposure may be delayed for months. Chronic exposure to MeHg may result in permanent CNS damage.

☐ **Permanent CNS damage may result from chronic exposure to MeHg.**

Laboratory Tests

Direct Biologic Indicators

Mercury can be measured in blood, urine, and hair. Since mercury has a short half-life in blood (3 days), blood analysis is typically performed shortly after an acute exposure; urine is the best biologic specimen when chronic mercury exposure is suspected. Hair analysis can provide evidence of MeHg exposure.

☐ **Blood is an appropriate specimen for analysis after acute mercury exposure; a 24-hour urine specimen is preferred in cases of chronic exposure.**

For acute high-level mercury exposure, whole blood is a valid indicator of body burden (and brain concentration of MeHg); for low-level exposure, plasma should be analyzed separately. Blood samples should be collected in vacutainers containing heparin and then refrigerated. In unexposed adults, the blood mercury level rarely exceeds 1.5 micrograms per deciliter (µg/dL); a blood concentration of 5 µg/dL or greater is considered the threshold for symptoms of toxicity.

☐ **In adults, the background mercury concentration is generally less than 1.5 µg/dL in blood and less than 20 µg/L in urine.**

A 24-hour urine specimen collected in an acid-washed plastic container is the preferred specimen for patients who have been chronically exposed to elemental mercury or mercury salts. A first morning void can provide a close approximation of a 24-hour collection, particularly if it is adjusted for the concentration of the urine (using specific gravity or amount of creatinine present). Since organic mercury is usually excreted through the biliary system, urine levels are not useful in evaluating MeHg exposure.

Urine should be analyzed for mercury by cold vapor atomic absorption spectrophotometry. The Reinsch test, a screening test for heavy metals, is not sufficiently specific or sensitive to detect low levels of mercury. A urinary mercury concentration of less than 20 µg/L in adults is considered background. Urine mercury concentrations from 20 to 100 µg/L are associated with subtle changes on some tests, even before overt symptoms occur (Table 2). Background or toxic urinary mercury concentrations have not been determined for children.

Generally, levels of mercury in hair are not useful in evaluating a patient clinically. A properly handled hair sample can provide evidence of MeHg exposure because MeHg accumulates in hair where its concentration remains constant. Maternal hair samples have been used to provide an estimate of fetal MeHg exposure.

Table 2. Relationship of urinary mercury concentration with effects

Urinary Mercury Concentration (µg/L)	Signs and Symptoms
<20	None
20 to 100	Decreased response on tests for nerve conduction, brain-wave activity, and verbal skills Early indication of tremor on testing
100 to 500	Irritability, depression, memory loss, minor tremor, and other nervous system disturbances Early signs of disturbed kidney function
500 to 1000	Kidney inflammation Swollen gums Significant tremor and nervous system disturbances

Indirect Biologic Indicators

If acute inorganic mercury poisoning is suspected, baseline BUN, creatinine, electrolytes, and urinalysis should be obtained; these values should be monitored continually to evaluate renal toxicity. Urinary β_2-microglobulin and retinol-binding protein levels may be useful in determining renal status. Liver function tests also should be performed.

Challenge

(4) *What problem list could you construct for the patient in the case study?*

(5) *What is your differential diagnosis?*

(6) *What tests would you order to confirm or rule out your diagnoses?*

Treatment and Management

The treatment of inorganic mercury poisoning usually involves the use of chelating agents. Chelating agents contain sulfhydryl groups, which bind mercury ions and facilitate their excretion through urine and feces. Dimercaprol (British anti-Lewisite or BAL) was the first chelating agent used for mercury toxicity and is still widely used for inorganic mercury poisoning. BAL is contraindicated for MeHg poisoning because it has been shown to increase the concentration of MeHg in the brain and therefore exacerbates symptoms. BAL is anticipated to be effective in treating phenylmercury poisoning because phenylmercuric acetate is rapidly oxidized to Hg^{2+} in the body; hence, phenylmercury is similar to inorganic mercury. Possible side effects of BAL include nausea and vomiting, headache, tachycardia, fever, conjunctivitis, blepharospasm, and lacrimation.

In some cases, an alternative or adjunct to parenterally administered BAL is orally administered N-acetylpenicillamine (NAP). Side effects of NAP can include fever, rash, leukopenia, eosinophilia, and thrombocytopenia.

☐ **Chelation therapy has been used successfully in treating patients who have ingested mercury salts or inhaled elemental mercury.**

☐ **No antidote exists for patients poisoned with organic mercury; supportive care is recommended.**

Newer derivatives of BAL, such as dimercaptosuccinic acid (DMSA) and 2,3-dimercaptopropane-1-sulfonate (DMPS), are more effective than BAL in experimental studies. DMSA (Succimer™[*]) is available in the United States; consult your regional certified poison control center or a physician experienced in chelation therapy for more information. DMPS is still an investigational drug and must be used under FDA guidelines. When DMPS was administered to two workers exposed to high levels of elemental mercury vapor, it decreased the mercury excretion half-life from 33.1 days to 11.2 days.

Elemental Mercury

- ☐ **Acute inhalation of mercury vapor may require chelation.**
- ☐ **Ingestion of elemental mercury in amounts typically found in thermometers does not usually require treatment.**

Patients who have experienced acute elemental mercury inhalation should receive supportive care; give supplemental oxygen as needed and monitor closely for development of acute pneumonitis and pulmonary edema. Chelation may be required.

Elemental mercury is usually nontoxic when ingested; the amount contained in a clinical thermometer typically presents little risk. In some circumstances, increased or enhanced absorption after a relatively small dose may occur in patients with inflammatory bowel disease. Rarely, mercury becomes trapped in the appendix or intestine and requires surgical removal.

To clean up a spill of metallic mercury, an ordinary household vacuum cleaner is of little use and may be harmful since it will vaporize the mercury and increase the airborne mercury concentration. Professional toxic clean-up with a self-contained vacuum system or a mercury clean-up kit should be used. Contaminated carpeting or porous tile should be discarded after clean-up.

Mercury Salts

- ☐ **Chelation therapy is recommended for serious systemic intoxication due to mercury salt ingestion.**

When a patient has ingested mercury salts, the goals of therapy are to remove mercury from the body and to prevent dehydration and shock. Inorganic mercury can be removed from the gastrointestinal tract by emesis, catharsis, or lavage. It is imperative that adequate intravenous fluids be administered to prevent dehydration and to reduce the concentration of mercury in the kidneys. BAL or other appropriate chelating agent should be administered immediately; its usefulness depends on rapid administration. With a potentially lethal mercury dose, early peritoneal dialysis or hemodialysis should be considered to enhance mercury removal and to support renal function.

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[*] Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

Organic Mercury

☐ **Administration of BAL for MeHg poisoning is contraindicated.**

Damage to the nervous system after MeHg exposure is usually permanent. Because of evidence that BAL increases the MeHg concentration in the brain, BAL (and perhaps other chelating agents) should not be used to treat MeHg toxicity. Since sulfhydryl groups bind tightly to mercury ions, oral polythiol resin (for mercury ingestion) and regional hemodialysis with L-cysteine may be of some benefit, but these therapies are unproven. Exchange transfusion also has been used in an attempt to reduce the body's mercury burden.

Challenge

(7) What treatment would you recommend for the patient in the case study?

(8) What follow-up measures would you recommend for managing this exposure?

Standards and Regulations

The regulations and guidelines pertaining to mercury and mercury compounds in air, water, and food are summarized in Table 3.

Workplace

Air

The workroom air standard mandated by the Occupational Safety and Health Administration (OSHA) is a time-weighted average (TWA) of 6.1 parts per billion (ppb) or 0.05 milligrams per cubic meter of air (mg/m^3) for inorganic mercury vapor, and 1.2 ppb or 0.01 mg/m^3 for organomercury compounds. NIOSH recommends a concentration no greater than 6.1 ppb as a TWA exposure for an 8-hour workday. Subjective psychological complaints, subtle decrements in some neuropsychological and neurophysiologic parameters, and the appearance of proteinuria have all been reported to occur after exposure to airborne mercury at concentrations as low as 1.2 ppb (0.01 mg/m^3). Correlating airborne mercury levels with health effects is difficult because almost all studies have used area sampling, rather than personal sampling, to determine air concentrations of mercury.

Environment

Air

The EPA National Emission Standards for mercury from various industrial sources include the following: mercury ore processing facilities—2300 g mercury maximum per 24-hour period; mercury cell chlor-alkali plants, sludge incineration plants, other wastewater treatments—3200 g mercury maximum per 24-hour period. Ambient air contains mercury at about 2.4 parts per trillion (ppt); however, concentrations near certain industrial areas, such as mercury mines and refineries, can be nearly 1800 ppt.

Water

The World Health Organization (WHO) guideline for all forms of mercury in drinking water is 1 ppb (1 µg/L). The EPA standard for drinking water is 2 ppb. EPA estimates that, for an adult of average weight, exposure to 21 µg of inorganic or organic mercury per day in food or water will probably not result in any harm to health. The FDA limits mercury in bottled water to 2 ppb.

Food

The FDA regulation for mercury in fish is 1 ppm (1000 ppb). Mercury concentrations in most non-fish foodstuffs are generally less than 0.02 ppb, although levels of up to 0.2 ppb have been detected in meat and poultry. The average concentration of mercury in most fish is less than 0.2 ppb.

Biologic Standards

Mercury is being considered for inclusion in the biological exposure indices (BEI) established by the American Conference of Governmental Industrial Hygienists (ACGIH). BEIs are reference values intended as workplace guidelines for evaluating potential exposure hazards by measuring appropriate determinants in specimens collected from workers at specified times. The proposed BEI for total inorganic mercury in urine, collected preshift, is 35 micrograms per gram (µg/g) creatinine. The proposed BEI for total inorganic mercury in blood is 1.5 µg/dL, collected at the end of the workweek.

Table 3. Standards and regulations for mercury

Agency[*]	Focus	Level	Comments
ACGIH	Air-workplace		
	Organo (alkyl) mercury compounds	1.2 ppb (0.01 mg/m^3)	Advisory; TLV-TWA[†]
		3.6 ppb (0.03 mg/m^3)	Advisory; STEL[§]
	Mercury vapor	6.1 ppb (0.05 mg/m^3)	Advisory; TWA
	Mercury (aryl and inorganic)	12 ppb (0.10 mg/m^3)	Advisory; TWA
NIOSH	Air-workplace	6.1 ppb (0.05 mg/m^3)	Advisory; TWA
OSHA	Air-workplace		
	Organo (alkyl) mercury compounds	1.2 ppb (0.01 mg/m^3)	Regulation; TWA
	Mercury vapor	6.1 ppb (0.05 mg/m^3)	
	Mercury (aryl and inorganic)	6.1 ppb (0.05 mg/m^3)	
EPA	Drinking water	2 ppb (2 μg/L)	Regulation; MCL[¶]
	Air		
	Mercury ore processing	2300 g Hg/24-hr period maximum	Regulation; National Emission Standard
	Mercury cell, chlor-alkali plants, sludge incineration and wastewater treatment plants	3200 g Hg/24-hr period maximum	
FDA	Food and water		
	Fish	1 ppm	Regulation
	Bottled drinking water	2 ppb (2 μg/L)	
WHO	Drinking water	1 ppb (1 μg/L)	Guideline

[*] ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; WHO = World Health Organization

[†] TLV-TWA (Threshold Limit Value-Time-Weighted Average) = a time-weighted average concentration for a normal workday and a 40-hour workweek to which nearly all workers may be repeatedly exposed

[§] STEL (Short-Term Exposure Limit) = a 15 minute TWA exposure which should not be exceeded at any time during a workday

[¶] MCL (Maximum Contaminant Level) = enforceable level for drinking water

Suggested Reading List

Reviews

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Friberg L, Vostal J, eds. Mercury in the environment: an epidemiological and toxicological appraisal. Cleveland, Ohio: CRC Press, 1987.

Goverment Documents

Agency for Toxic Substances and Disease Registry. Toxicological profile for mercury. Atlanta: US Department of Health and Human Services, Public Health Service, 1989.

Environmental Protection Agency. Mercury health effects update; health issue assessment. Washington, DC: Government Printing Office, 1984; DHEW publication no. 8-84-019F.

Sources of Information

More information on the adverse effects of mercury and the treatment and management of mercury-exposed persons can be obtained from ATSDR, your state and local health departments, university medical centers, and the National Pesticide Telecommunications Network 24-hour toll-free hotline (1-800-858-7378). *Case Studies in Environmental Medicine: Mercury Toxicity* is one of a series. For other publications in this series, please use the order form on the back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of the Director, at (404) 639-6204.

Answers to Pretest and Challenge Questions

Pretest

Pretest can be found on page 1.

(a) The patient's problem list includes painful extremities; erythematous and peeling skin on nose, toes, and fingers; personality changes; tachycardia; sweating; and possible intermittent low-grade fever.

(b) Diagnoses you might consider are the following:

(1) acute rheumatic fever. ARF occurs most commonly between the ages of 5 and 15 years when streptococcal infection is relatively common. Sore joints and fever are characteristic.

(2) leukemia. This is the most common cancer in young children, and symptoms can include sweats and low-grade fever. This diagnosis would not explain the erythematous and peeling skin of the fingers and toes.

(3) Kawasaki disease. The patient does not have some of the common signs of this disease: e.g., he does not have bilateral conjunctivitis; lymphadenopathy; a red rash on his body; red and sore lips, mouth, or throat. However, he is under 5 years of age and does have red and tender hands and feet with peeling skin. He may have had a fever, but it is not well characterized. Kawasaki disease is relatively rare—only 5 to 10 of every 100,000 children acquire the disease.

(4) tuberculosis. The patient's night sweats and possible low-grade fever make this a possibility; however, he has no cough, and tuberculosis is not associated with erythematous and peeling skin on the fingers and toes.

(5) measles. Although immunized against measles, the patient could have experienced primary vaccine failure. However, he does not have Koplik's spots, cough, conjunctivitis, coryza, or a typical rash, making this diagnosis unlikely.

(6) boric acid poisoning. Irritability and erythema and peeling of the skin and mucous membranes can occur with boric acid poisoning. However, the patient does not exhibit renal toxicity or other common symptoms of boric acid toxicity such as nausea, vomiting, and diarrhea.

(7) acrodynia. The patient exhibits many of the symptoms common to this disease. See the problem list in (a) above. This disease of infancy and early childhood is caused in most, if not all, instances by exposure to mercury.

In addition, Stevens-Johnson syndrome, fifth disease, scarlet fever, rubella, systemic lupus erythematosus, and drug rashes (due to an unsuspected ingestion) should be considered.

(c) The best test to confirm or rule out chronic mercury exposure is a 24-hour urinary mercury concentration and creatinine clearance. The urine should be analyzed by cold vapor atomic absorption spectrophotometry; the Reinsch test—a heavy metal screening test—is not sufficiently specific or sensitive. In addition, the following tests would be useful to help exclude other diagnoses in the differential: complete blood count with differential; erythrocyte sedimentation rate or C-reactive protein; chest and hip X rays; serum creatinine and blood urea nitrogen; urinalysis; tuberculin skin test with controls; streptoccocal antibody titers (ASO); and throat culture for streptococcus.

Answers to Pretest and Challenge Questions

Pretest *continued*

(d) If test results indicate the patient has a high urinary mercury concentration, chelation therapy should be considered, and a physician experienced in chelation therapy should be consulted. It is also important to ensure that the patient is no longer exposed to the mercury source.

All family members should have their urinary mercury concentration measured. A common exposure is quite likely, particularly if the source is mercury vapor in the home. If the source is a product used in the home, other persons using the product may be at risk. The county or state health department should be contacted to identify and eliminate the mercury source and to evaluate the potential exposure to members of the community. Medical follow-up for mercury-exposed persons includes monitoring nervous system and renal function status.

Challenge

Challenge questions begin on page 4

(1) In a patient so young, sources of chronic mercury exposure are most likely to be linked to the home. Within the home, the possible mercury sources include off-gassing of paint on interior walls and liquid mercury from a spill embedded in floors or carpets. Possible ingestion sources include contaminated drinking water, mercury-containing medicinals, or folk remedies.

(2) If the mercury source is in the home or diet, all members of the family could be exposed. Other persons in the community who ingest contaminated food or drink might also be affected. In addition, if paint is the source of exposure, consumers using the same paint brand may be exposed.

(3) Yes, if the source is elemental mercury vapor released from paint in the home, the mother, and subsequently, the fetus, are likely to be exposed. Although the adverse developmental effects of MeHg are known, the long-term neurologic consequences to the human fetus of chronic low-level exposure to mercury vapor have not been documented well.

(4) See pretest answer (a).

(5) See pretest answer (b).

(6) See pretest answer (c).

(7) See pretest answer (d).

(8) See pretest answer (d), paragraph 2.

ATSDR
July 1992
Case Studies in Environmental Medicine

20

Methanol Toxicity

Environmental ALERT . . .

☑ ***Methanol toxicity initially lacks severe toxic manifestations. Its pathophysiology represents a classic example of "lethal synthesis" in which toxic metabolites cause fatality after a characteristic latent period.***

☑ ***Methanol is sometimes used as an ethanol substitute by alcohol abusers.***

☑ ***The shift to alternative motor fuels may significantly increase both acute and chronic methanol exposures in the general population.***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. See page 21 for more information about continuing medical education credits and continuing education units.

Guest Contributor: *Dennis Shusterman, MD, MPH*
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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

A 67-year-old man with headache, nausea, and visual disturbance

During an afternoon visit, you see a 67-year-old man for onset of headache, nausea, and visual disturbance. The friend who accompanies him explains that both of them frequent the same senior center and that they have been preparing for a fund-raising event during the past 2 days. During this time, the patient spent between 6 and 9 hours per day reproducing fliers using a "spirit duplicator" (mimeograph machine). This activity took place in a small, unventilated room with the patient working alone most of the time.

On questioning, the patient says that he had eye irritation and lightheadedness after the first few hours of activity but considered these symptoms to be a minor annoyance. He also had nausea by the end of the first day but noted that this cleared overnight. During the second day of activity, he was again troubled by eye irritation, this time accompanied by vertigo, tinnitus, visual blurring, and photophobia. He tried to ventilate the room by placing a small fan near the door but continued to feel poorly despite a prolonged break. Late in the afternoon his friend insisted that he seek medical attention.

The patient is a widower and retired insurance salesman with a smoking history of one pack per day from age 27 to 62 (none for the last 5 years). He typically consumes a six-pack of beer per day, but he has felt poorly and has been abstinent for the past 10 days. Medical history includes coronary artery bypass surgery at age 63 with subsequent medical management of stable angina and a transurethral prostatectomy at age 65 with no recurrence of obstructive symptoms. Current medications include nitroglycerine patches used before exercise (with no patches used in the previous 4 days) and sublingual nitroglycerine, which he takes rarely. The review of symptoms is negative for other cardiopulmonary complaints. There is no family history of glaucoma, myopia, or diabetes mellitus.

On examination, the patient is alert and oriented to time, space, and person, although he appears somewhat distracted. His breath has a faint solvent-like smell. Vital signs are within normal range with the exception of a respiratory rate of 30/minute. The cardiopulmonary examination is unremarkable, but abdominal examination reveals mild tenderness in the epigastrium without rebound or guarding. Muscle tone, strength, sensation (pinprick, light touch, position sense) and reflexes are symmetrically intact. His gait is unsteady with a wide-based stance, and he shows a positive Romberg sign, heel-to-shin, and rapid alternating movements (bilaterally).

Ophthalmologic examination reveals a visual acuity of 20/200 bilaterally despite newly prescribed corrective lenses. The conjunctivae appear somewhat injected, nystagmus is present on lateral gaze, and the pupils are large and poorly reactive to light. Examination also reveals hyperemia of the optic nerve head with no hemorrhages or exudates.

Pretest

(a) What is the differential diagnosis for this patient?

(b) What additional information would you request regarding the patient's activities in the last 2 days?

(c) What consultation(s) would you obtain to help you manage this case?

(d) What type of therapeutic intervention is indicated?

Answers can be found on page 17.

Exposure Pathways

- ☐ **Methanol is used in a variety of commercial and consumer products.**
- ☐ **Increased use of methanol as a motor fuel may cause higher ambient air levels and a greater potential for ingestion from siphoning accidents.**

Methanol (methyl alcohol) is a clear, colorless, flammable liquid with a faintly pleasant odor. Popularly known as wood alcohol, methanol has historically been referred to as wood spirit, wood naphtha, pyroligneous spirit, and carbinol. Despite these references to its derivation as a wood distillation product, methanol is currently produced almost exclusively by synthetic pathways. It ranks 22nd (by volume) among chemicals produced in the United States.

The largest quantities of methanol are used for the manufacture of other chemicals including methyl methacrylate, acetic acid, ethylene glycol, and methyl chloride. Methanol also is added to a variety of commercial and consumer products such as windshield washing and deicing solutions (35% to 95% concentration), duplicating fluids (95% concentration or greater), solid canned fuels (4% concentration), paint removers, model airplane fuels, and embalming fluids. Other methanol uses are as a denaturant for ethanol; as a solvent for shellacs, lacquers, adhesives, and inks; and, most recently, as an alternative motor fuel. Because methanol is a natural fermentation product, its concentration may be up to 300 milligrams per liter (mg/L) in wines and higher in brandies and other distilled fruit spirits. Although serious methanol toxicity has been most commonly associated with ingestions, exposures also occur via inhalation and skin absorption, which are a concern in both occupational and household settings.

Environmentally, methanol has been detected in concentrations ranging from less than 10 parts per billion (ppb) in rural air to nearly 30 ppb in urban air. If methanol-powered vehicles become more prevalent, ambient methanol levels could be thousands of times greater in residential and public parking garages. Currently, there is no enforceable atmospheric standard for methanol. Increased use of methanol as a motor fuel would probably result in the reduction of some air pollutants (e.g., particulates and ozone) but an increase in others (e.g., formaldehyde). Data regarding methanol levels in drinking water are lacking.

Challenge

(1) In emergency situations, what reference sources could you use to aid in identifying the chemical constituents of consumer and commercial products such as the duplicating fluid used in the case study?

Who's at Risk

According to estimates from the National Institute for Occupational Safety and Health (NIOSH), more than 2.5 million persons are regularly exposed to methanol on the job. Workers most likely to experience inhalation or skin exposures to methanol include bookbinders, bronzers, dyers, foundry workers, gilders, hatmakers, ink makers, laboratory technicians, painters, photoengravers, and chemical manufacturers. In addition, administrative aides or others using mimeograph machines may be exposed to methanol, as well as workers at refineries, fuel distribution centers, and service stations, if they handle methanol-containing fuels.

Householders, hobbyists, and motorists using methanol-containing products can be at risk for inhalation exposure; therefore, precautions must be taken to avoid using these products in poorly ventilated spaces. In addition, prolonged skin contact with methanol can produce systemic effects—a painter developed blindness after working in methanol-soaked clothes, and an 8-month-old child with a methanol-soaked pad placed on his chest developed signs of methanol toxicity.

Historically, the largest number of serious methanol exposures have occurred by ingestion. Methanol poisoning has been caused by materials such as shellac thinner, duplicator fluid, and denatured alcohol that have been drunk directly or have been used to adulterate beverages. In addition, about 35,000 gasoline ingestions are reported annually in the United States, most of which occur from fuel siphoning. Siphoning accidents could significantly increase the number of methanol ingestions if the use of methanol-containing automotive fuels becomes widespread.

One step in the metabolic detoxification of methanol is a folic acid-dependent process. Consequently, susceptibility to methanol toxicity may be higher among folate-deficient persons. Folate deficiency can occur not only in persons consuming inadequate diets, but also in those with intestinal malabsorption (e.g., inflammatory bowel disease) or hemolytic anemia, or in persons undergoing drug therapy (e.g., anticonvulsants, antibiotics). Because alcoholics have a greater likelihood of both methanol ingestion and folate deficiency, they may be at dual risk for methanol's adverse effects. Up to 10% of the population may be folate-deficient.

☐ **Persons having prolonged skin contact with methanol are at risk of developing severe systemic effects.**

☐ **Persons ingesting adulterated alcoholic beverages are at great risk of methanol toxicity.**

☐ **Folate-deficient persons are potentially at increased risk for toxicity after methanol exposure.**

Challenge

Additional information for the case study: During the investigation, you request a listing of the contents on the label of the duplicating fluid used by the patient. You learn that it contains greater than 90% methanol. You also learn that the patient drank a small amount of the duplicating fluid (about 5 milliliters [mL]) on his second day of working at the senior center.

(2) Discuss the factor(s) that may place this patient at increased risk of methanol toxicity.

Biologic Fate

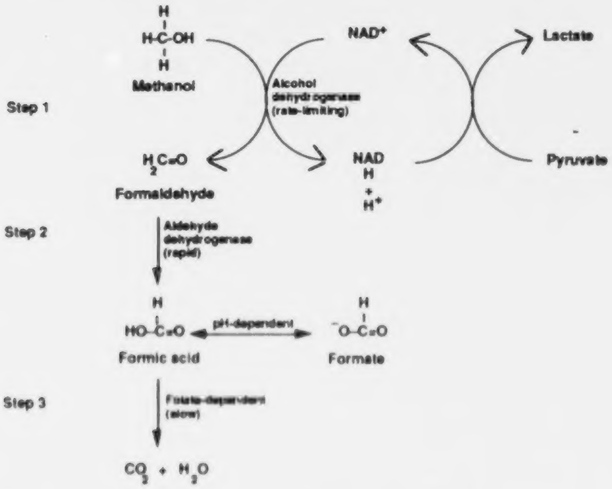
- ☐ **Methanol is absorbed well by all exposure routes.**
- ☐ **Methanol is oxidized in the liver to formaldehyde, then formic acid, which contributes to the profound metabolic acidosis seen in acute methanol poisoning.**
- ☐ **Most methanol is eliminated via the lungs as carbon dioxide.**

Gastrointestinal absorption of methanol is virtually complete, whereas lung retention averages 58%. Dermal absorption may occur if skin is abraded or methanol exposure is prolonged. There is evidence that methanol absorption through the skin is enhanced in gasoline-methanol mixtures. Once absorbed, methanol is distributed with total body water.

Metabolism of methanol is a three-step process taking place chiefly in the liver. The first metabolic step involves methanol's oxidation to formaldehyde by alcohol dehydrogenase, which is a saturable, rate-limiting process (Figure 1, Step 1). In the next step (Figure 1, Step 2), formaldehyde is oxidized by aldehyde dehydrogenase to formic acid (or formate, depending upon pH). Since step 2 is rapid, little formaldehyde accumulates in the serum. Formic acid, a metabolite of formaldehyde, contributes to the development of metabolic acidosis both directly (i.e., via its acid load) and indirectly (i.e., through its inhibitory effects upon iron-containing cytochromes with subsequent accumulation of lactic acid [lactate]). In Step 3, formic acid is detoxified to carbon dioxide and water.

Some absorbed methanol is eliminated unchanged via the lungs (10% to 20%) and kidneys (about 3%). However, most absorbed methanol is oxidatively metabolized (75% to 85%). A small amount of the metabolic products is excreted in the urine as formate, but most is exhaled as carbon dioxide. Methanol elimination patterns are dose-dependent, with elimination half-lives ranging from 3 hours in volunteers who ingested small amounts of methanol to 30 hours in persons who overdosed.

Figure 1. Methanol metabolism to toxic intermediates—formaldehyde and formic acid (formate).


Step 1
Methanol
NAD+
Lactate
Alcohol dehydrogenase (rate-limiting)
Formaldehyde
NADH + H+
Pyruvate
Step 2
Aldehyde dehydrogenase (rapid)
pH-dependent
Formic acid
Formate
Step 3
Folate-dependent (slow)
CO2 + H2O

Discovery of methanol's metabolic pathway has led to several practical treatments; among them are the therapeutic administration of ethanol and folic acid. Alcohol dehydrogenase, the enzyme responsible for the first step of methanol metabolism, has an approximately ninefold greater affinity for ethanol than for methanol. Administration of ethanol blocks the oxidation of methanol, preventing the lethal synthesis of formaldehyde and formic acid and increasing the amount of methanol that is eliminated unchanged (now approximately equal amounts in urine and exhaled breath). Administration of folic acid and its analogues, which affect Step 3, enhances the conversion of toxic formic acid to carbon dioxide and water (Figure 1).

Physiologic Effects

Acute Exposure

Methanol shares with many other hydrocarbon solvents the ability to produce reversible sensory irritation, headache, nausea, and narcosis at airborne levels below those producing specific organ system pathology. Headaches were a frequent complaint in one study of office workers in the vicinity of duplicating machines where airborne methanol levels were in the range of 200 to 375 parts per million (ppm). In another study, exposed administrative aides were

☐ **The acute effects of inhaling methanol vapor, which are similar to those caused by many other organic solvents, include upper respiratory tract irritation and inebriation.**

☐ **The metabolic products of methanol can produce a syndrome of delayed-onset acidosis, obtundation, visual disturbance, and death.**

☐ **Partial or total blindness, dementia, or a Parkinson-like syndrome are potential sequelae in survivors of acute methanol intoxication.**

significantly more likely to report blurred vision, headache, dizziness, and nausea than were controls. Workers reported that the symptoms improved when they were away from the workplace.

Most methanol-related metabolic and ophthalmologic alterations have been associated with exposure through ingestion. Although the most frequently cited dosage for a lethal methanol ingestion is 1 milliliter per kilogram (mL/kg) of body weight, permanent blindness and deaths have been reported with ingestions as low as 0.1 mL/kg (6 to 10 mL in adults).

Metabolic Effects

After a characteristic latent period of 6 to 30 hours, severe metabolic acidosis may occur in victims of methanol poisoning. The acidosis is due to formic acid, and less often, lactic acid. Formic acid is metabolically produced from methanol, while lactic acid results from hypotension and from formate's interference with cellular respiration.

Ophthalmologic and Neurologic Effects

Experimental evidence suggests that formate is responsible for optic nerve damage in methanol overexposure. In fatal cases, the optic nerve shows central necrosis in the distal (orbital) portion with the central optic tracts intact. In nonfatal cases, visual function can normalize completely after treatment, although central and peripheral scotomata or complete blindness may persist, depending on several variables. Occasional neurologic sequelae of methanol poisoning can include polyneuropathy, a Parkinson-like extrapyramidal syndrome, and mild dementia. Hemorrhages in the putamen have been documented on computerized tomography (CT) scanning and on pathologic examination.

Chronic Exposure

Respiratory and Ophthalmologic Effects

☐ **Chronic exposures to methanol have not been thoroughly studied, although anecdotal reports of chronic visual effects have been published in the medical literature.**

Despite methanol's widespread use, there are few rigorous studies of workers chronically exposed to methanol. Some reports can be found of permanent visual effects due to chronic inhalation or dermal exposure, but many of these reports date to the early part of the century and lack exposure data. Inhalation studies in experimental animals do not demonstrate significant pathology with chronic exposures at levels up to 50 times the current occupational Permissible Exposure Limit (PEL) of 200 ppm. The only consistent effects in rats and monkeys exposed for 4 weeks to levels up to 5000 ppm methanol vapor were mucoid nasal discharge and upper respiratory tract irritation; no ophthalmologic alterations were found. Because formic acid is rapidly metabolized and does not accumulate in experimental animals, they may not be good models for the ophthalmologic effects of methanol.

Other Effects

Published data on animal and human developmental effects of methanol are limited and inconclusive. One case-control study of pregnant women in the workplace shows a possible association of fetal central nervous system defects with exposures to a mixed solvent that included methanol. The general medical literature contains no references to methanol's carcinogenic potential in humans.

- ☐ **Data regarding the potential developmental effects of methanol exposure are inconclusive.**
- ☐ **Data regarding the carcinogenic potential of methanol in humans are lacking.**

Challenge

(3) Do the symptoms and appearance of the patient in the case study suggest acute methanol intoxication? Explain.

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____

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Clinical Evaluation

History and Physical Examination

History-taking in methanol intoxications should focus on exposure route. In suspected ingestions, the clinician should ask about the consumption of illicit alcoholic beverages (or beverages that may have been adulterated) and about other potential accidental or intentional ingestion scenarios. In suspected inhalational and dermal exposures, emphasis should be placed on identifying specific methanol-containing products (e.g., canned fuel, windshield washer solution, duplicator fluid, shellac thinner, alternative fuels) and on documenting unusual conditions of prolonged and extensive skin contact or inhalation. The symptom history should emphasize disturbances in visual, neurologic, and gastrointestinal function. The physical examination should focus particularly on neurologic status and ocular findings.

- ☐ **In cases of suspected methanol intoxication, the goal is to determine exposure route and neurologic and ocular status.**

Signs and Symptoms

Acute Exposure

☐ **Timely evaluation of a patient who may be overexposed to methanol is essential to prevent severe and permanent sequelae.**

Persons acutely exposed to high levels of methanol via ingestion, inhalation, or extensive skin contact may develop severe metabolic, ocular, and neurologic toxicity. The initial intoxicating effects of methanol are similar to those of ethanol in producing cognitive slowing and cloudy sensorium, which extends to impaired brain stem function at very high doses. After a latent period of 12 to 24 hours, methanol toxicity may result in progressive visual disturbance and impairment of consciousness due to the gradual build-up of toxic metabolites. Unusual ocular symptoms, such as a sensation of "being in a snowstorm," may be reported. Ophthalmologic examination may reveal central or peripheral visual field defects and dilated pupils that react poorly to light but accommodate normally. Erythema of the optic nerve may occur, with peripapillar edema early in the course. Rarely, flame-shaped hemorrhages may be seen. Necrosis of the distal portion of the optic nerve leads to atrophy, which may be evidenced by optic nerve pallor days or weeks after exposure.

Chronic Exposure

☐ **Symptoms of chronic, low-level methanol exposure are generally reversible.**

Persons intermittently or chronically exposed to airborne methanol at levels insufficient to cause systemic acidosis may complain of eye irritation and visual blurring, upper respiratory irritation, headache, nausea, and lightheadedness—all of which are reversible under these conditions. Chronic short-term cutaneous exposures may result in skin irritation and defatting. Chronic ingestion of methanol at levels documented in commercially distilled beverages or in drinking water have not been linked with specific symptoms or pathology.

Laboratory Tests

In light of methanol's profound metabolic effects, numerous standard laboratory tests are useful in documenting acute toxicity. These include the following:

Blood methanol and blood ethanol
Arterial blood gases
Serum electrolytes (Na^+, K^+, Cl^-, HCO_3^-) and calculation of
  anion gap
BUN and serum creatinine
Serum glucose
Serum ketones
Serum osmolarity and calculation of osmolar gap
Urinalysis
CBC

Direct Biologic Indicators

Although methanol can be detected in both urine and exhaled breath, blood methanol levels are more widely available and serve as the best predictor of toxicity immediately after acute exposure. The normal blood concentration of methanol from endogenous sources is less than 0.05 milligrams per deciliter (mg/dL). Generally, central nervous system effects appear above blood methanol levels of 20 mg/dL; ocular symptoms appear above 100 mg/dL; and fatalities in untreated patients have occurred in the range of 150 to 200 mg/dL.

After the latency period, blood methanol level alone is not a reliable prognostic indicator because toxicity results from the metabolites. A methanol level below 20 mg/dL in a symptomatic patient, for example, does not rule out serious intoxication since the methanol may already have been completely metabolized to formate. When considerable time has elapsed after ingestion, mortality correlates best with severity of acidosis rather than with blood methanol levels.

In the workplace, where intermittent or chronic exposures are likely to occur, the American Conference of Governmental Industrial Hygienists (ACGIH) recommends a urinary methanol level of less than 15 mg/L at the end of an 8-hour workshift.

☐ **Immediately after an acute exposure, a blood methanol level serves as the best predictor of the severity of the clinical course.**

☐ **Chronic methanol exposure can be documented by measuring urinary methanol.**

Indirect Biologic Indicators

Of methanol's metabolites, only formate is present in biologic fluids at concentrations useful for monitoring exposures. When serum formate levels exceed 20 mg/dL, ocular injury and metabolic acidosis are likely. In acute intoxications, elevated serum formate concentrations can confirm the diagnosis and aid in clinical decisionmaking regarding the institution of hemodialysis. However, laboratory tests for serum formate levels are not widely available.

The ACGIH considers a urinary formic acid level of less than 80 milligrams per gram (mg/g) creatinine, obtained preshift at the end of a workweek, as indicative of exposures below the 8-hour time-weighted average (TWA) of 200 ppm.

The anion gap and osmolar gap aid in the diagnosis of acute methanol poisoning. The serum anion gap (AG) may be defined by the formula

$$AG = (Na^+ + K^+) - (Cl^- + HCO_3^-)$$

with all ions measured in milliequivalents per liter (mEq/L). The normal anion gap is 12 to 16.

☐ **Formate levels are useful as indicators of methanol exposure, although they are not widely available.**

☐ **Both the anion and osmolar gaps are increased in methanol poisoning.**

An approximation of the serum osmolar gap (OG) is most commonly defined as

$$OG = \text{Osmolarity (measured)} - (2\ Na^{+} + [BUN \div 2.8] + [\text{Glucose} \div 18])$$

with measured osmolarity expressed in milliosmoles per liter (mOsm/L), Na^{+} in mEq/L, and BUN and glucose in mg/dL. The normal osmolar gap is 0 to 10.

The conditions that can produce an elevated anion-gap acidosis are summarized by the mnemonic MUDPILES:

M	Methanol intoxication
U	Uremia
D	Diabetic ketoacidosis
P	Propylene glycol poisoning
I	Iron and isoniazid overdoses; inhalants (carbon monoxide, cyanide, hydrogen sulfide)
L	Lactic acidosis
E	Ethanol (alcoholic) ketoacidosis, ethylene glycol poisoning
S	Salicylate overdose

Of the various pathophysiologic states and toxic agents listed above, only diabetic ketoacidosis, ethanol ketoacidosis, and methanol and ethylene glycol poisoning produce elevations of both the anion and osmolar gaps. Identification of diabetic ketoacidosis is based on the findings of elevated serum glucose and ketones, particularly in a person with pre-existing diabetes mellitus. Ethanol ketoacidosis is characterized by a history of chronic, excessive ethanol intake with anorexia and vomiting and acidosis out of proportion to the apparent degree of ketonemia.

Differentiation of methanol and ethylene glycol poisoning is based on the exposure history and on specific toxicologic testing. In ethylene glycol poisoning, there is an absence of eye complaints; oxalate crystals are found in the urine; and hypocalcemia may be present.

Findings that may accompany secondary complications of methanol poisoning include myoglobinuric renal failure (with elevations in serum creatinine and CPK, a positive test for occult blood in the urine, and rare or absent red blood cells in the urine sediment), pancreatic or salivary gland pathology (with hyperamylasemia), and central nervous system pathology (as evidenced by diffuse cerebral edema or hemorrhages of the putamen on CT scanning). Mean corpuscular volume (MCV) is elevated in severe methanol poisoning, probably resulting from a primary increase in red blood cell size from poisoning rather than megaloblastic anemia.

Challenge

(4) *The patient in the case study has a serum sodium of 140, potassium 4.0, chloride 102, and bicarbonate 10 (all measured in mEq/L). The glucose level is 90 mg/dL, BUN 14 mg/dL, and measured osmolarity 320 mOsm/L. What is the calculated anion gap? Osmolar gap? Are these gaps consistent with methanol poisoning?*

(5) *What is the differential diagnosis for a wide anion-gap acidosis?*

(6) *What conditions can produce an elevated serum osmolar gap?*

(7) *What neuro-ophthalmologic findings might be anticipated in the patient?*

Treatment and Management

Acute Exposure

Acute methanol intoxication constitutes a medical emergency. Effective therapy requires attention to both clinical and laboratory data, as well as anticipation of events that may be latent at the time of initial examination. Methanol intoxication, like that of ethylene glycol, acetaminophen, and lithium, may deceive the clinician by the initial lack of severe toxic manifestations.

For recent, suspected methanol ingestions, gut decontamination should be carried out even in the absence of clinical or laboratory abnormalities. Emesis should be induced if the patient is conscious and if a substantial ingestion has occurred within 30 to 45 minutes of first medical care; alternatively, gastric lavage may be performed, particularly if the patient is obtunded. There is no evidence that activated charcoal or cathartics significantly reduce methanol absorption.

Formate's diffusion across cell membranes, particularly in the optic nerve, is facilitated by a low systemic pH; hence, therapy should include partial correction of acidosis via direct alkalinization. Intravenous sodium bicarbonate therapy, which is aimed at reversing acidosis (by titrating the blood pH) to avert circulatory collapse and

☐ **With methanol poisoning, substantial treatment delays may occur because the clinician is falsely reassured by the initial lack of severe symptoms.**

☐ **Intravenous sodium bicarbonate therapy should be considered if the blood pH is below 7.2.**

☐ **Symptoms and history determine whether intravenous ethanol therapy and hemodialysis should be instituted.**

impede the intracellular penetration of formic acid, should be considered if the pH is below 7.2. A reduction of blood pH of 0.15 corresponds to a base deficit of 10 mEq/L bicarbonate. The target should be a pH in the range of 7.36 to 7.40. Sodium bicarbonate solution should be administered slowly to allow the resulting carbon dioxide to dissipate via hyperventilation. Sodium overload is a constant hazard of sodium bicarbonate therapy, and electrolytes must be monitored frequently.

In cases of suspected methanol exposure, the following are indications for starting an intravenous ethanol infusion: a blood methanol level of greater than 20 mg/dL; a history of ingesting more methanol than 0.4 mL/kg body weight; any ingestion history, with delayed access to toxicologic testing; or metabolic acidosis with otherwise unexplained elevated anion and osmolar gaps, especially if eye symptoms are present. Ethanol, usually as a 10% solution (10 mL of 100% ethanol in 90 mL of 5% aqueous dextrose), is first administered intravenously in a loading dose of approximately 7.5 to 10 mL/kg over 20 to 60 minutes. If the patient is conscious, oral loading doses can be given since intravenous doses may be painful.

The subsequent ethanol infusion rate varies with the patient's ethanol metabolism and should be adjusted to keep the blood ethanol level between 100 and 150 mg/dL. Typically, rates between 0.8 to 1.4 mL/kg/hr suffice. In chronic alcoholics and during hemodialysis (see paragraph below), higher rates may be required. Infusions are continued until the methanol level drops below 20 mg/dL.

Criteria for combined ethanol infusion and hemodialysis include visual disturbance, or a methanol level exceeding 50 mg/dL, or a severe acidosis unresponsive to intravenous bicarbonate. Peritoneal dialysis is less effective than hemodialysis in clearing methanol from the blood. During hemodialysis, ethanol infusions should not only continue, but also should be increased slightly to compensate for the increased ethanol clearance. Even during dialysis, the target blood ethanol concentration should remain at 100 to 150 mg/dL.

An adjunctive treatment for methanol poisoning is the administration of folate (in the form of folic acid or folinic acid) to increase the conversion of formate to carbon dioxide and water. Folate administration is considered safe and may be efficacious if the patient is folate-deficient. Suggested dosage regimens include folic acid, 50 to 70 mg intravenously every 4 hours for the first 24 hours of treatment, or folinic acid (also known as leucovorin, Citrovorum factor, or 5-formyl-5,6,7,8-tetrahydrofolate), 1 to 2 mg/kg intravenously every 4 to 6 hours. Any attempt to replenish folic acid stores by administering multiple vitamins is likely to be frustrated by their low folate content (typically 1 mg per tablet).

An experimental drug, 4-methylpyrazole, is being investigated in animals and humans. This orally administered drug, which combines with the enzyme alcohol dehydrogenase, may replace ethanol as a safe means to block methanol metabolism while patients are prepared for hemodialysis. Administration of 4-methylpyrazole does not appear to add to the patient's CNS depression as does ethanol. In addition, the metabolism of 4-methylpyrazole is more predictable and prolonged than is that of ethanol, making administration less difficult technically. Investigation of 4-methylpyrazole is currently in Phase I in the United States.

Chronic Exposure

Because a clearly defined clinical syndrome does not exist for chronic methanol exposure, treatment should be symptomatic. Patient management should include removal from exposure, supportive counseling, and a consideration of alternative diagnoses.

☐ **Patients chronically exposed to methanol should be treated symptomatically.**

Challenge

Additional information for the case study: Consistent with acute methanol intoxication, the patient's arterial blood gases indicate a pH of 7.25; bicarbonate is 10 mEq/L, pCO_2 23 mm Hg, and pO_2 92 mm Hg. The blood methanol level is 83 mg/dL.

(8) What type of therapeutic intervention is indicated?

(9) You are a rural practitioner, and the nearest hospital is 90 minutes away by ambulance. Although you stock standard intravenous rehydration solutions in your clinic pharmacy and have a "crash cart" with standard resuscitative drugs, there is no intravenous ethanol or parenteral folate available. There is, however, a liquor store nearby. If vodka is used as a substitute for ethanol, explain how you would prepare the ethanol dosing solution.

Standards and Regulations

- ☐ **Currently, EPA does not regulate the amount of methanol in public drinking water supplies.**
- ☐ **EPA has not promulgated an air emission standard for methanol.**
- ☐ **OSHA regulations for worker exposures to methanol include a requirement that skin contact be minimized.**

Workplace

Air

Methanol is volatile at room temperature and has an odor threshold at approximately 100-250 ppm concentration in air. The Occupational Safety and Health Administration (OSHA) maintains a workplace limit for airborne exposures to methanol of 200 ppm (as an 8-hour TWA) and 250 ppm for short-term (15-minute) excursions not to exceed four such excursions in an 8-hour day (Table 1). Identical standards are recommended by ACGIH and NIOSH. The odor of methanol may not be perceived by some persons until levels exceed acceptable workplace limits. Concentrations exceeding 25,000 ppm are considered "immediately dangerous to life or health" (i.e., they may result in irreversible health effects or impair the ability of an individual to escape from the exposure environment). In general, airborne exposures can be controlled through engineering measures or by appropriate personal protective equipment or both.

Significant dermal absorption of methanol can occur. Workers using methanol should be protected against dermal exposures by engineering controls (e.g., by isolating the work process) and by using personal protective equipment (impervious gloves, aprons, boots, and other appropriate equipment).

Environment

Air

EPA does not have an emission standard for methanol. However, under EPA's generic standards for the synthetic organic chemical manufacturing industry, all volatile organic chemical (VOC) emissions, including methanol releases, are to be kept to a technologically feasible minimum.

Drinking Water

Neither EPA nor the states maintain standards for methanol in drinking water.

Table 1. Standards and regulations for methanol

Agency[*]	Focus	Level	Comments
OSHA	Air-workplace	200 ppm	Regulation: PEL[†] (8-hr TWA[‡])
		250 ppm	Regulation: PEL (STEL[§])
NIOSH	Air-workplace	200 ppm	Advisory: REL[**] (8-hr TWA)
		250 ppm	Advisory: REL (STEL)
ACGIH	Air-workplace	200 ppm	Advisory: TLV[††] (8-hr TWA)
		250 ppm	Advisory: TLV (STEL)
EPA	Air-environment	N/A	Covered under the "best available technology" clause for VOC emissions from new or modified facilities.
	Water-drinking	N/A	
FDA	Food	N/A	Approved only as an "indirect food additive" (i.e., in food packaging adhesives).

[*] ACGIH = American Conference of Governmental Industrial Hygienists, EPA = Environmental Protection Agency; FDA = Food and Drug Administration, NIOSH = National Institute for Occupational Safety and Health, OSHA = Occupational Safety and Health Administration

[†] PEL (Permissible Exposure Limit) = highest level of methanol in air to which a worker may be exposed during a normal workshift

[‡] TWA (Time-Weighted Average) = time weighted average concentration for a normal 8-hour workday and 40-hour workweek to which nearly all workers may be repeatedly exposed

[§] STEL (Short-Term Exposure Limit) = usually a 15-minute sampling period. In the case of methanol, not to exceed four 5-minute excursions in an 8-hour workday, with at least 1 hour between excursions

[**] REL (Recommended Exposure Limit) = highest recommended level of methanol in air to which a worker may be exposed during a normal workshift

[††] TLV (Threshold Limit Value) = exposure guideline recommended by ACGIH

Suggested Reading List

Environmental Sources and Routes of Exposure

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Related Government Document

National Institute for Occupational Safety and Health. Criteria for a recommended standard: occupational exposure to methyl alcohol. Washington, DC: US Department of Health, Education and Welfare, 1976; Publication no. (NIOSH) 76-148. NTIS no. P8-273 806/0.

Sources of Information

More information on the adverse effects of methanol and treating and managing cases of exposure to methanol can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Methanol Toxicity* is one of a series. For other publications in this series, please use the order form on the back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of the Director, at (404) 639-6204.

Answers to Pretest Questions and Challenge Questions

Pretest questions begin on page 1. Challenge questions begin on page 2.

Answers to Pretest

(a) Acute visual loss in this age group can occur with central retinal artery or vein occlusion, internal carotid emboli, vitreous hemorrhage, retinal/macular hemorrhage, retinal detachment, temporal arteritis, cerebrovascular accidents of the posterior circulation, acute angle-closure glaucoma, idiopathic optic neuritis, head trauma, and carbon monoxide and methanol poisoning. Of these conditions, only cerebrovascular events, head trauma, temporal arteritis, and carbon monoxide and methanol poisoning commonly affect vision bilaterally. Other symptoms such as hyperpnea, and later, Kussmaul breathing, are indicative of acidosis (see page 10 for a differential diagnosis of acidosis). The patient also manifests signs of inebriation. Methanol poisoning could account for all of these effects.

(b) The following information should be sought in any occupational or avocational history: (1) a full description of the activity in question, with identification of all chemical products used (including ethanol) either by chemical or trade name; (2) documentation of potential routes of exposure including inhalation, skin contact, and ingestion; and (3) type of ventilation employed and use of personal protective equipment.

(c) Confirmation of suspected methanol poisoning should take place in an emergency department or inpatient setting with rapid laboratory tests and the opportunity for prompt therapeutic intervention. Physicians with special expertise who might be consulted in this case include clinical toxicologists, nephrologists, and ophthalmologists. In geographic areas with restricted access to specialists or with exposures of questionable toxicologic significance, informational assistance can be obtained from the nearest regional poison control center.

(d) The clinical findings and the acknowledged methanol exposure (see Challenge question 2, page 4) are indicative of methanol intoxication of potentially life-threatening severity. Appropriate therapeutic interventions for methanol intoxication include intravenous ethanol infusion, sodium bicarbonate and folate administration, and hemodialysis.

In addition, the patient should receive psychosocial care for his substance abuse tendencies. Referral to a substance abuse program is appropriate.

Answers to Challenge Questions

(1) In emergency situations, the most complete and up-to-date information is usually available through a regional poison control center. Common reference books that contain information on the chemical composition of consumer and commercial products include Gosselin's *Clinical Toxicology of Commercial Products* and Sax's *Dangerous Properties of Industrial Materials*, among others. Many local hospital emergency departments have access to toxicologic reference information either on microfiche or CD-ROM. Some hospital libraries also have access to online clinical toxicology databases.

(2) The patient used a methanol-containing product for an extended period in a small, unventilated room. Thus, the inhaled dose alone is significant. The patient also admits to ingesting a small amount of the product. Furthermore, as an alcohol abuser, the patient may be folate-deficient, thus increasing his risk of methanol toxicity.

(3) Yes, the symptoms and appearance of the patient in the case study do suggest acute methanol intoxication. The patient manifests symptoms of inebriation and complains of visual disturbance several hours after the start of a significant methanol exposure. He also is showing signs of acidosis. These factors constitute a classic presentation for acute methanol intoxication.

(4) The calculated anion gap is 32 (normal: 12 to 16) and the calculated osmolar gap is 30 (normal: less than 10). These values are consistent with acute methanol intoxication. For calculations, see below.

$$\text{Anion Gap} = (Na^+ + K^+) - (Cl^- + HCO_3^-)$$
$$= (140 + 4) - (102 + 10)$$
$$= 144 - 112$$
$$= 32$$

$$\text{Osmolar Gap} = \text{Osmolarity (measured)} - (2Na^+ + [BUN \div 2.8] + [Glucose \div 18])$$
$$= 320 - (2 \times 140 + [14 \div 2.8] + [90 \div 18])$$
$$= 320 - (280 + 5 + 5)$$
$$= 320 - 290$$
$$= 30$$

(5) The conditions that can produce an elevated anion-gap acidosis are summarized by the mnemonic MUDPILES:

M	Methanol intoxication
U	Uremia
D	Diabetic ketoacidosis
P	Propylene glycol poisoning
I	Iron and isoniazid overdoses; inhalants (carbon monoxide, cyanide, hydrogen sulfide)
L	Lactic acidosis
E	Ethanol (alcoholic) ketoacidosis, ethylene glycol poisoning
S	Salicylate overdose

(6) Intoxication by the following agents (or accumulation, in the case of acetone in diabetic or alcoholic ketoacidosis) produces an elevated osmolar gap: methanol, ethanol, ethylene glycol, acetone, and isopropanol.

Although several drugs can potentially contribute to the osmolar gap (e.g., salicylates, paraldehyde, and chloral hydrate), they are rarely present at concentrations sufficient to raise osmolarity.

(7) A neuro-ophthalmologic examination of the patient might reveal several findings. Results of examination of visual fields, as determined by perimetry, typically indicate central scotomata early in the course of methanol poisoning (soon after onset of acidosis), with peripheral constriction of visual fields a late finding. Dilated, unreactive pupils and dim vision are characteristic. The result can be bilateral blindness, which is usually permanent.

(8) See the answer to Pretest question (d) above.

(9) One-hundred proof vodka is actually 50% ethanol by volume. A loading dose equivalent to the required 7.5 mL/kg of 10% ethanol can be achieved with vodka as follows: In a 70 kg person, a total of 525 mL of 10% ethanol would be needed (7.5 mL/kg × 70 kg = 525 mL).
525 mL × 10% = X mL × 50%
52.5 mL = 0.5X mL
X = 105 mL of the 50% ethanol
In summary, 105 mL of 50% ethanol with 5% dextrose in water added to total 525 mL will produce a 10% ethanol solution. (See *Treatment and Management*, page 11.) This quantity of vodka or an equivalent amount of ethanol from another distilled spirit can be initially administered orally or by gavage.

ATSDR **June 1990**

Case Studies in Environmental Medicine

3

Methylene Chloride Toxicity

Environmental ALERT . . .

☑ ***The effects of acute exposure to methylene chloride (dichloromethane) are due to its CNS depressant properties, which have resulted in fatalities.***

☑ ***Metabolic conversion of methylene chloride to carbon monoxide may place persons with pre-existing coronary artery disease at increased risk.***

☑ ***EPA considers methylene chloride to be a probable human carcinogen.***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. The Agency for Toxic Substances and Disease Control (ATSDR) and the Centers for Disease Control (CDC) designate this continuing medical education activity for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association and 0.1 continuing education units for other health professionals. See pages 19 to 21 for further information.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

Confusion and chest pain in a 67-year-old paint stripper

A 67-year-old male patient has been brought by his wife and a neighbor to the hospital emergency room on a weekend while you are on call. Complaining of headache and chest pain, he is unable to provide additional information because of his confusion and disorientation. His wife states that he retired 2 years ago and has been relatively vigorous and in good health since. His principal activities have been house repairs and gardening. He was in his usual state of health, including normal mental alertness for his age, until approximately 2 weeks ago.

Over the past 2 weeks, his wife noted progressive loss of mental alertness and increasing fatigue and lethargy, becoming much worse in the evening. He usually sleeps 8 hours a night, but in the past 2 days he has been slow to rise even after 10 hours of sleep. She has noticed that he has become increasingly slow to respond, has slurred speech, and has mood swings from extremely happy to sad or anxious. Yesterday she found him wandering in various rooms of the house and in the yard. Upon questioning, he did not remember why he was in those particular places. He called her a number of times to find tools that he had misplaced, which was unlike him. When she asked him today how he was feeling, for the first time he mentioned having headache and chest pain, but he could not remember when they began.

A review of the history provided by his wife reveals that the patient has mild degenerative arthritis in his fingers and hips, for which he takes an over-the-counter variety of ibuprofen. He was evaluated for occasional chest discomfort at age 55, including a treadmill stress test that his wife believes was negative. At that time, a diagnosis for the chest pain was not determined, and the pain resolved without medication. He was hospitalized in his twenties for an appendectomy. He smoked a pack of cigarettes a day from age 20 to age 55, at which time he quit smoking. They have two children and five grandchildren, all alive and well. His parents have been dead for many years; his wife believes that they had some "heart problems."

For the past 2 weeks he has been working, as he has often done in the past, on home repairs and in the garden. He has a basement workshop; his wife knows that he has been preparing some furniture for repainting. She states, "My husband and our neighbor spend many hours on projects and like to be left alone." She believes that he has been working for approximately 2-hour intervals, removing paint from the furniture. He has also been tending to their lawn; he spread fertilizer once 2 weeks ago, and at least once since then has dusted their roses with what she thinks is a fungicide. The garden materials are stored in their basement.

On physical examination, you find a well-nourished, somewhat anxious and disheveled man, appearing his stated age. He is well-tanned and mildly diaphoretic. His blood pressure is 145/80, pulse is 110 and regular, and temperature is normal. He has slurred speech and 15- to 20-second delays in responding to questions. He is oriented only to person, requires concentration for an approximate identification of place, and is disoriented to time. He has little recall of either recent or past events and cannot perform serial numbers. The rest of his physical examination is unremarkable, except for tachycardia with a fourth heart sound. There are no focal neurological findings. An electrocardiogram shows sinus tachycardia and a 1-mm depression of the ST segment in lead V_3. A complete blood count, chemistry panel, arterial blood gases, and urinalysis are within normal limits.

Upon conferring with the emergency physician, you administer sublingual nitroglycerin during electrocardiographic monitoring. The patient reports relief of chest pain, and the ST segment depression returns to normal. You have him admitted to the coronary care unit for observation.

Pretest

What should be included in this patient's problem list? ______

What is the differential diagnosis for this patient? ______

What tests would you order to confirm or rule out these diagnoses? ______

Answers are incorporated in Challenge answers (7) through (9).

Exposure Pathways

☐ **Because of its high lipid solubility, nonflammability, and high vapor pressure, methylene chloride is used in many important industrial processes and consumer products.**

☐ **Nonoccupational exposures to methylene chloride occur mainly through hobby and household uses of paint strippers and aerosol sprays.**

☐ **Principal route of exposure is inhalation.**

Methylene chloride (dichloromethane) is a clear, colorless liquid with a mild, sweet odor that can be detected at concentrations of 100 to 300 parts per million (ppm). It is neither flammable nor explosive at room temperature. Methylene chloride is also known as DCM, methylene di- (or bi-) chloride.

Methylene chloride is lipophilic and is an excellent solvent for many resins, waxes, and fats; it has many industrial applications as a component in

aerosol propellants or carrier solvents
paint and varnish thinners and removers
certain paints and adhesives
fire extinguishers

and as a process chemical in the manufacture of

synthetic fibers
photographic film
polycarbonate plastics
pharmaceuticals
printed circuit boards
inks

Methylene chloride is also used as a blowing agent for urethane foams, an extractant for foods and spices, a grain fumigant, a metal degreaser and cleaner, and a low-pressure refrigerant.

Exposures to the highest concentrations of methylene chloride are generally occupational; more than a million workers have significant potential for exposure. Nonoccupational exposures may occur through ambient air or groundwater contaminated by facilities that manufacture, use, store, or dispose of methylene chloride, or from consumer products that contain methylene chloride as a solvent, flame retardant additive, or propellant. The highest nonoccupational exposures probably occur during paint stripping by hobbyists and in the household use of aerosol sprays. Aerosol propellants may contain up to 50% methylene chloride and are commonly used with hair sprays, antiperspirants, air fresheners, and spray paints. Studies have not associated health effects with the low levels of methylene chloride present in decaffeinated coffees and spices after extraction, or with those in chlorinated drinking water.

The principal route of human exposure is inhalation. Skin absorption is usually small because of rapid evaporation; however, trapping the liquid against the skin with clothing or gloves can lead to greater absorption and, occasionally, serious chemical burns.

Challenge

(1) The patient's neighbor remembers similar symptoms in a man with whom he worked during his years as a painter; that coworker had been stripping paint from doors. What does this information suggest?

(2) In light of (1) above, what specific information would be useful in making a diagnosis?

Who's at Risk

Because the highest exposure levels of methylene chloride occur in the workplace, workers in certain industries (see page 2) are at higher risk of adverse health effects. Persons living near methylene chloride production-and-use facilities or near hazardous waste sites that store methylene chloride may have increased risk of exposure from chemical emissions. Methylene chloride released to the atmosphere readily disperses, so air contaminated by point sources is less of a hazard than contamination of the groundwater.

Methylene chloride may remain in groundwater for years and can be widely distributed. From here it may be ingested in drinking water or inhaled as it volatilizes from the water during activities such as showering and laundering.

☐ **Workers and residents near industrial facilities that produce, use, store, or dispose of methylene chloride have an increased risk of exposure.**

☐ **Users of certain consumer products may also experience exposure to high levels of methylene chloride for short periods of time.**

- ☐ **Persons with preexisting cardiovascular disease may be at increased risk due to methylene chloride exposure.**
- ☐ **Carbon monoxide produced by the metabolism of methylene chloride may have adverse consequences on fetal development.**

In nonindustrial settings, transitory high-level exposures to methylene chloride occur in poorly ventilated areas where adhesives, aerosols, paint strippers, and paint thinners are in use. Exposures to moderately elevated levels of methylene chloride during occasional product use are not expected to cause adverse health effects in normal, healthy persons.

Since carbon monoxide is a metabolite (see Biologic Fate), exposure to methylene chloride can produce tissue hypoxia. In persons with coronary artery disease, this may result in angina pectoris or myocardial infarction. Physical exercise during exposure increases the risk to such patients.

Persons with already elevated carboxyhemoglobin levels from other sources may also be affected because the metabolism of methylene chloride adds to the total body burden of carbon monoxide. Two common sources of exogenous carbon monoxide are smoking and occupations that involve exposure to exhaust from internal combustion engines. Forklift drivers, diesel mechanics, and tunnel workers, for instance, are susceptible to such exposures.

Animal studies have shown that methylene chloride readily crosses the placenta and can enter breast milk. It is not known if the developing human fetus is at increased risk from the direct effects of unmetabolized methylene chloride. Indirect effects from increased levels of maternal carbon monoxide produced by the metabolism of methylene chloride, however, may have adverse consequences on fetal development.

Challenge

(3) Does the patient described in the case study fit the profile of a person at increased risk for adverse effects from methylene chloride exposure? Explain.

Biologic Fate

Once methylene chloride has been ingested or inhaled, it is readily absorbed through the lungs and gastrointestinal tract. Dermal exposure also results in absorption, but at a slower rate than other exposure routes.

Factors affecting the methylene chloride body burden are exposure level and duration, route of exposure, physical activity, and amount of body fat. In volunteer human subjects, exposures to air levels of 50 to 200 ppm caused the concentration of methylene chloride in the blood to increase linearly with the ambient air concentration. With increasing exposure level, blood saturation occurs and the concentration of methylene chloride in blood reaches a plateau.

Following absorption, methylene chloride is distributed mainly to the liver, brain, and subcutaneous adipose tissue. The liver is the primary site of metabolism, although additional transformation occurs in the lungs and kidneys. In the liver, methylene chloride may undergo metabolism by two pathways. The first pathway produces carbon monoxide (CO) and carbon dioxide (CO_2) and is saturable at a few hundred ppm. The second pathway yields formaldehyde and formic acid and shows no indication of saturation at inhaled concentrations to 10,000 ppm.

The metabolic contribution of each pathway appears to vary in humans, particularly with the exposure level; therefore, toxicity extrapolation between high and low doses is complex. Furthermore, recent studies suggest that the second pathway is considerably more active in certain animal species, particularly mice, a finding that complicates interspecies comparisons.

The metabolic formation of carbon monoxide and its subsequent binding to hemoglobin, producing carboxyhemoglobin (CO-Hb), may continue for several hours after cessation of methylene chloride exposure, as fat and other tissues continue to release accumulated amounts of the lipophilic solvent. This endogenous release of methylene chloride, therefore, prolongs the duration of cardiovascular stress to about twice that caused by a comparable CO-Hb level resulting from exposure to exogenous carbon monoxide.

The body eliminates methylene chloride primarily through the lungs. A small amount of unchanged methylene chloride is also eliminated in urine and feces. At low doses, a large percentage of methylene chloride is metabolized and eliminated as carbon monoxide, while at higher doses more of the unchanged parent compound is exhaled.

☐ **Because of its high lipid solubility, methylene chloride is readily absorbed and quickly distributed throughout the body.**

☐ **At high levels of exposure, much of the methylene chloride that is inhaled is exhaled unchanged.**

☐ **At low-level exposures, the primary metabolites of methylene chloride are carbon monoxide and carbon dioxide; at higher levels, formaldehyde and formic acid are also formed.**

Challenge

(4) Additional information for the case study: You request an inventory of the chemicals in your patient's workshop. Examination of the materials brought in by the neighbor reveals the following:

*"ACM" * brand paint stripper, consisting of 80% methylene chloride, 15% mineral spirits, and 5% methanol*
*"Best Bud" * brand rose dust, containing benomyl as the active ingredient*
*"Gro-tall" * brand inorganic fertilizer*
No insecticides, specifically no organophosphates or carbamates, were found.

Explain how the paint stripper might have caused your patient's cardiac symptoms.

(5) Could the use of the rose dust or fertilizer be related to your patient's condition?

---

*The use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services

Physiologic Effects

Acute Exposure

☐ **The primary effects of inhaled methylene chloride are a result of its narcotic action.**

The major adverse health effect associated with short-term exposure to methylene chloride at high concentrations is depression of the central nervous system. In some cases with exposure over 8000 ppm, unconsciousness, narcosis, and occasionally death due to respiratory depression have occurred. Lower concentrations (300 to 800 ppm in air) have resulted in impairment of sensory (visual, auditory) and psychomotor functions. The CNS effects are generally reversible and are thought to be due to methylene chloride alone or in combination with metabolically released carbon monoxide, but not to carbon monoxide alone.

Other effects of acute exposure include irritation of the eyes and upper respiratory tract, cardiac effects (myocardial ischemia, dysrhythmia) and, very rarely, pulmonary irritation and edema. No substantial human hepatic or renal effects have been reported after an acute exposure to methylene chloride. Skin contact with methylene chloride may cause dermatitis; prolonged skin contact can result in chemical burns. Corneal burns may follow direct eye splashes.

Chronic Exposure

Sequelae of chronic methylene chloride exposures have not been fully determined. Data from epidemiologic studies suggest that there may be serious long-term health effects from chronic exposure to methylene chloride in the form of pancreatic, hepatic, or biliary tract cancer. These occupational data are not sufficient to allow a clear interpretation, however (see Carcinogenic Effects below).

☐ **Recent evidence suggests that serious long-term effects may result from chronic exposure to methylene chloride.**

Cardiovascular Effects

Since exposure to methylene chloride increases the CO-Hb level in the blood, it is expected to have an additive effect on CO-Hb levels produced from other sources. Under normal conditions, the blood contains less than 1% CO-Hb, while a one-pack-a-day smoker will generally have a CO-Hb level of 4% to 5%, and a heavy smoker, 8% to 12%. With exposure to methylene chloride at levels of 500 ppm (the permissible workplace limit) and above, the CO-Hb level has been reported to reach 15% or more in smokers. These CO-Hb levels are below those considered hazardous for most normal, healthy persons but could place additional stress on persons with coronary artery disease or angina. It is well documented that elevation of the CO-Hb level to greater than 2% to 3% saturation can adversely affect such patients. In addition, a recent study of bridge and tunnel workers found an increased incidence of cardiovascular disease, which suggests that long-term, relatively low carbon monoxide exposure may affect cardiovascular risk.

☐ **Persons with coronary artery disease or angina may not be able to tolerate the added cardiovascular stress brought on by carbon monoxide that is metabolically released from methylene chloride.**

Despite animal inhalation studies that suggest exposure to methylene chloride lowers the myocardial threshold to the arrhythmogenic action of injected epinephrine, there is no direct evidence for such an effect in humans. In one study, 24 healthy workers chronically exposed to methylene chloride at concentrations averaging from 60 to 475 ppm were electrocardiographically monitored and showed neither an increase in ventricular or supraventricular ectopic activity nor episodic ST segment depression. Likewise, there was no evidence of cardiac susceptibility or electrographic abnormalities in several case reports of otherwise healthy persons rendered unconscious from acute exposure to methylene chloride. There are no studies that address this arrhythmogenic effect in persons with underlying coronary disease.

Hepatic Effects

Liver toxicity has not been reported in epidemiologic studies, and it appears that serious hepatic effects would only occur in exposures above current permissible workplace levels. One case of hepatitis and several cases of elevated liver enzymes in exposed workers have been documented. Inhalation studies have demonstrated methylene chloride causes hepatic neoplasms in animals.

☐ **Methylene chloride has been associated with mild hepatotoxicity in humans.**

Carcinogenic Effects

☐ **Methylene chloride may be a carcinogenic risk to humans.**

A long-term (1964-1984) epidemiologic study of workers chronically exposed to methylene chloride during the manufacture of photographic products reported no statistically significant excesses in deaths from lung or liver cancer or from ischemic heart disease. The investigators did, however, report an increased incidence of pancreatic cancer deaths (8 compared with 3.1 expected; median latency 30 years). A more recent epidemiologic study of employees in a fiber production plant has reported an excess of liver and biliary tract cancer deaths among methylene chloride-exposed workers. In both studies, however, the data are not adequate to draw a firm conclusion. Risk of developing cancer from chronic methylene chloride exposure cannot be ruled out.

Methylene chloride has been reported to produce benign mammary tumors and malignant liver and lung neoplasms in several animal species. The metabolic pathway in at least one species of these animals is known to be different from that in humans. Nevertheless, on the weight of the evidence, EPA considers methylene chloride a probable human carcinogen.

Reproductive and Developmental Effects

☐ **Methylene chloride itself does not appear to pose a threat to human reproduction or fetal development. Metabolically released carbon monoxide, however, could be potentially harmful to the developing fetus.**

No data were found in the available literature on potential reproductive or developmental effects of methylene chloride in humans. Like many other organic solvents, methylene chloride can reach the human fetus through the placenta and can enter human breast milk. Maternal carbon monoxide levels may have an effect on the developing fetus. It has been assumed that the association of low fetal birth weight with mothers who smoke is primarily due to increased levels of maternal carbon monoxide.

Challenge

(6) *Could exposure to methylene chloride be the cause of progressive loss of mental acuity, increasing fatigue, lethargy, slurred speech, and mood swings in the patient described in the case study? Explain.*

Clinical Evaluation

History and Physical Examination

A medical history and physical examination are the first steps in evaluating those exposed to methylene chloride. The medical history should include items known to reflect methylene chloride exposure; the physical examination should include evaluation of the central nervous and cardiovascular systems, pancreas, and liver. The medical history should emphasize the following:

- family history, particularly coronary artery disease
- occupational history
- hobbies or household projects, particularly furniture refinishing, spray painting, paint stripping
- location of residence and workplace in relation to industrial facilities
- source of drinking water supply

☐ **Assessment of methylene chloride-exposed persons should include evaluation of the CNS, cardiovascular system, pancreas, and liver.**

Signs and Symptoms

Acute Exposure

Methylene chloride exposures at levels below the odor threshold for up to 8 hours have produced no adverse health effects in humans. At levels of exposure at or above the odor threshold, reported effects include the following:

- euphoria
- sluggishness
- light-headedness
- irritability
- sleepiness
- dizziness

At exposure levels above 500 ppm, the following may also be present:

- headache
- impairment of concentration and coordination
- loss of balance
- irritation of eyes, nose, and throat
- nausea
- flushing
- confusion
- slurred speech
- ischemic heart pain
- respiratory distress or failure to maintain the airway during CNS depression
- pulmonary edema (rare)

☐ **Signs and symptoms of acute methylene chloride toxicity are generally those due to CNS depression.**

Table 1 represents a compilation of data from case reports in the literature and summarizes reported symptoms with accompanying exposure levels and duration. At exposure levels over 8000 ppm, unconsciousness has been reported; levels over 50,000 ppm have been reported to be immediately life-threatening. Delayed CNS effects could occur after recovery from severe poisoning.

Table 1. Human symptoms and potential airborne concentrations

Effect	Concentration	Exposure Duration
ACGIH[*] TLV[†]	50 ppm	8 hours
Odor threshold	100-300 ppm	On exposure
OSHA[*] PEL[§]	500 ppm	8 hours
No acute effects	100-280 ppm	Up to 7.5 hours
Altered responses on sensory and psychomotor tests	300-800 ppm	At least 40 minutes
Light headedness	500-1000 ppm	1 to 2 hours
Irritation, dizziness	2300 ppm	5 minutes
Nausea	2300 ppm	30 minutes
Headache, fatigue, irritation	Up to 5000 ppm	Time of onset not specified (noted during 2-year average occupational exposure)
Paresthesia, irritation	7200 ppm	8 minutes
Narcosis	8000-20,000 ppm	30 minutes to 4 hours
Immediately dangerous to life or health	>50,000 ppm	Immediate

[*] ACGIH = American Conference of Governmental Industrial Hygienists; OSHA = Occupational Safety and Health Administration

[†] TLV (Threshold Limit Value) = the time-weighted average concentration for a normal 8-hour workday and 40-hour workweek, to which nearly all workers may be repeatedly exposed.

[§] PEL (Permissible Exposure Limit) = highest level of methylene chloride in air, averaged over an 8-hour workday, to which a worker may be exposed.

Adapted from A.H. Hall and B.H. Rumack, presentation at the American Association of Poison Control Centers/American Academy of Clinical Toxicology/American Board of Medical Toxicology/Canadian Association of Poison Control Centres Annual Scientific Meeting, Baltimore, MD, October 1-4, 1988.

Chronic Exposure

☐ **Early signs of chronic methylene chloride exposure are likely to be similar to those of acute exposure.**

Early signs and symptoms of chronic methylene chloride exposure are not well documented, but are likely to reflect CNS depression. The following have been reported by workers with repeated exposure: headache, dizziness, nausea, memory loss, paresthesias in hands and feet, mental and physical fatigue, and loss of consciousness. In persons with preexisting coronary artery disease or angina, signs and symptoms of angina pectoris and myocardial ischemia may occur.

Laboratory Tests

Biologic monitoring of chronically exposed workers is often based on direct indicators such as methylene chloride in breath, blood, or urine samples. Monitoring of carboxyhemoglobin levels and liver function tests can also be used. A panel of tests that may aid in evaluating the health of a patient with methylene chloride exposure is presented below.

Standard Tests

- Carboxyhemoglobin level
- Arterial blood gases
- Electrolyte panel
- CBC
- Hepatic enzyme levels (SGOT or AST, SGPT or ALT)
- Urinalysis
- Creatinine
- Cardiac evaluation (cardiac enzymes and serial electrocardiograms)

Specialized Tests

- Methylene chloride levels in breath, blood, or urine (if exposure is recent)

Direct Biologic Indicators

Methylene chloride can be detected in exhaled breath up to several hours postexposure. Breathing ambient levels of 200 ppm methylene chloride will result in about 80 ppm in expired air. The methylene chloride concentration in exhaled air will generally reflect the amount inhaled at ambient levels up to about 500 ppm. The concentration of carbon monoxide in alveolar air also has been found to correlate with methylene chloride levels in ambient air up to 200 ppm.

☐ **Methylene chloride can be assayed in breath, blood, or urine.**

☐ **Carboxyhemoglobin and the metabolite formic acid can be measured in blood and urine, respectively.**

Methylene chloride can be directly measured in the blood shortly after exposure. Of the methylene chloride absorbed, 25% to 90% is eliminated within 2 hours after exposure; 16 hours after exposure, none will be detected in the blood. Interpretation of methylene chloride blood levels is difficult. Workers exposed to currently permissible concentrations usually have blood levels of 1 to 2 µg/mL. There are only a few blood levels reported in the literature, and these are for patients with either fatal or serious poisonings, allowing little comparison.

Carboxyhemoglobin, which forms as a result of methylene chloride metabolizing to carbon monoxide, can be detected in blood of nonsmokers about 30 minutes after methylene chloride exposure.

Ambient air concentration of approximately 200 ppm of methylene chloride corresponds to carboxyhemoglobin levels of 4% to 9%, similar to levels found in smokers. Exposure to about 500 ppm for several hours results in CO-Hb levels as high as 15%. Since many factors can contribute to elevated CO-Hb levels, including exercise, smoking, and exogenous exposure to carbon monoxide, the CO-Hb level may not correspond directly to inhaled levels of methylene chloride. Urinary levels of formic acid, an intermediate product in the metabolism of methylene chloride, have been used to monitor exposed workers.

Indirect Biologic Indicators

☐ **There is currently no known indirect biologic indicator that correlates with methylene chloride exposure.**

Other than CNS effects, short-term, moderate-level exposures to methylene chloride do not appear to cause any measurable changes in biologic parameters. Possible long-term effects include hepatic function abnormalities.

Challenge

(7) You find that the patient described in the case study is suffering from mental confusion. What are some likely causes of this condition in the elderly?

(8) Initially, you ordered a chemistry panel, CBC, and arterial blood gas tests, the results of which are within normal limits. How do these findings help in your diagnosis?

(9) The status of subsequent laboratory tests follows. How do you interpret this information?

Blood CO-Hb level at least 4 hours after last exposure is 15%
Blood methylene chloride level will be available in 1 week
Liver function test results are consistent with mild hepatocellular dysfunction
CPK isoenzymes, cardiac enzymes, and serial ECGs appear normal

Treatment and Management

Acute Exposure

To treat acute toxic exposures, immediately remove the person from the source of exposure and give oxygen or artificial respiration, if indicated. Contaminated clothes should be removed and the exposed skin washed with soap and water. Symptomatic eye exposure requires saline irrigation and inspection for corneal damage. In cases of ingestion, the efficacy of syrup of ipecac, lavage, charcoal, or cathartics is not known.

☐ **Life-sustaining procedures and supportive care are the only known treatments for those acutely exposed to methylene chloride.**

Acute toxic effects may persist for hours after removal from the source of exposure because of continued metabolism of methylene chloride released from tissue storage. Carboxyhemoglobin levels can continue to rise, peaking 5 to 6 hours after exposure. Peak levels have been generally reported to be as high as 25%. Oxygen is the primary therapy. The half-life of CO-Hb in room air is 5.3 hours but this can be reduced to 60 to 90 minutes in 100% oxygen. At high CO-Hb levels, hyperbaric oxygen will reduce the half-life to 20 to 40 minutes. The use of steroids and mannitol for cerebral edema has been recommended, but their value in preventing late neurologic sequelae remains unproven. Because of possible cardiovascular involvement, monitoring for dysrhythmias is indicated. Baseline liver function tests with periodic monitoring to detect possible hepatic toxicity should be performed.

Proper use of paint strippers and other methylene chloride-containing products should be discussed with patients. The importance of adequate ventilation or respiratory protection and other protective equipment while using these products should be explained. It would also be prudent to advise patients with coronary artery disease or angina to avoid all exposure to such products.

Chronic Exposure

There are no known antidotes to methylene chloride and no methods for enhancing the direct elimination of methylene chloride from the body. Most CNS effects due to short-term chronic exposure will resolve when the patient is permanently removed from the source of exposure. If the CO-Hb level is significantly elevated, then the patient should be treated by administering oxygen, as discussed above. Evidence for the usefulness of tests to determine long-term CNS injury, including psychological and neurologic studies, is conflicting.

☐ **Patients chronically exposed to methylene chloride should be treated symptomatically.**

Challenge

(10) What is the treatment for methylene chloride intoxication?

(11) What is the prognosis for the patient described in the case study?

Standards and Regulations

Table 2 (page 15) summarizes the standards and regulations for methylene chloride, which are discussed below.

Workplace

Air

☐ **OSHA's permissible exposure limit is currently under review.**

The Occupational Safety and Health Administration (OSHA) established a time weighted average (TWA) standard of 500 ppm (8-hour workday, 40-hour workweek) to prevent acute narcosis and liver injury. In 1986, OSHA issued a notice of proposed rulemaking to lower this standard; to date, no official action has been taken.

In 1976, the National Institute for Occupational Safety and Health (NIOSH) recommended a threshold limit value (TLV) of 75 ppm on the basis of an acceptable CO-Hb level of 5% or less at the end of an 8-hour shift. Today, NIOSH considers methylene chloride to be a possible human carcinogen and recommends the "lowest feasible limit" of exposure.

The American Conference of Governmental Industrial Hygienists (ACGIH) has recommended that its TLV-TWA of 100 ppm, first proposed in 1981, be lowered to 50 ppm. The new ACGIH guideline is designed to reduce carcinogenic risk and avoid excessive levels of CO-Hb.

Table 2. Standards and regulations for methylene chloride

Agency[*]	Focus	Level	Comments
ACGIH	Air-Workplace	50 ppm	Advisory; TWA[†]; to avoid carcinogenic risk
NIOSH	Air-Workplace	N/A	Advisory; lowest feasible level
OSHA	Air-Workplace	500 ppm	Regulation; PEL[§] as TWA[†]
EPA	Air-Environment	N/A	Under review; proposal scheduled for June, 1990
FDA	Cosmetics	0	Regulation; ban became effective in 1989
	Food	10 ppm	Regulation; residual in decaffeinated coffee

[*] ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration

[†] TWA (Time-Weighted Average) = time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek to which nearly all workers may be repeatedly exposed.

[§] PEL (Permissible Exposure Limit) = highest level of methylene chloride in air, averaged over a normal workday, to which a worker may be exposed.

Environment

Air

The Office of Toxic Substances (OTS) within EPA promulgates regulations related to manufacturers and processors of chemicals that may present an unreasonable risk to health or the environment. The OTS has initiated a priority review of human cancer risks from certain exposures to methylene chloride; no regulation has emerged to date.

☐ **EPA has not promulgated an emission standard for methylene chloride.**

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Water

☐ **EPA currently has no standard regulating the amount of methylene chloride in public drinking water supplies.**

The EPA Office of Drinking Water projects that a standard for methylene chloride will be proposed in June 1990.

Food

☐ **FDA has banned the use of methylene chloride in cosmetics.**

The Food and Drug Administration (FDA) has recently reviewed the risks to humans of exposure to methylene chloride. The outcome was a ban on the use of this chemical as an ingredient of cosmetic products. The FDA continues to permit the use of methylene chloride as an extraction solvent for decaffeinating coffee, with an allowable residual concentration up to 10 ppm in the decaffeinated coffee.

Other

☐ **CPSC is reviewing the use of methylene chloride in consumer products.**

The use of methylene chloride in spray paints and paint strippers for household use is under review by the Consumer Product Safety Commission (CPSC).

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Answers to Pretest and Questions

Pretest is on page 1. Challenge questions begin on page 3.

(1) Since both your patient and the former coworker described by the neighbor were removing paint from wood, it is reasonable to suspect the product used for that purpose could have caused the symptoms noted.

(2) You could ask your patient's wife or neighbor to examine the contents of the workshop, and bring in the labels or containers of any materials that the patient may have used over the past 2 weeks. Even if inconvenient, it can be more productive to have someone inspect the patient's environment, rather than relying on laboratory tests. You could also ask a public health official to examine the patient's workshop.

(3) To the extent the patient's history and risk factors indicate possible coronary artery disease or angina, he would fit the profile of one at increased risk from methylene chloride exposure.

(4) Methylene chloride constitutes 80% of the paint stripper, and because of its high volatility, could reach a significant ambient level in a poorly ventilated area such as a basement workshop. Methylene chloride is metabolized in part to carbon monoxide, sometimes producing elevated carboxyhemoglobin (CO-Hb) levels when overexposure occurs. Continued production of CO-Hb during gradual release of methylene chloride from adipose tissue may lead to prolonged tissue hypoxia, resulting in cardiac ischemia, particularly when coronary artery disease is already present. The other constituents of the paint stripper, mineral spirits and methanol, are also anesthetic agents, but in these concentrations have likely contributed only slightly to your patient's mental confusion.

(5) No. It is unlikely that the rose dust or fertilizer contributed to your patient's symptoms. The fertilizer is an inorganic material that could cause eye, nose, or throat irritation, but when applied in the normal fashion, has no other toxic effects. Benomyl is a fungicide of extremely low acute toxicity.

(6) Yes. Methylene chloride is a general anesthetic (central nervous system depressant). The patient's mental condition is of subacute onset and duration and is consistent with overexposure to an organic solvent such as methylene chloride.

(7) Besides cardiac ischemia, your patient's problem list includes a mentally confused state that may be classified as either delirium or dementia. The distinguishing factors between these two conditions are (a) onset and duration and (b) state of consciousness. Delirium has a more acute onset and shorter duration (lasting several hours to days) and is characterized by a variable clouding of consciousness, usually worsening at night. Such states are not uncommon in the elderly. It is important when confronted with such a patient that the physician look for a treatable cause.

(8) The existing laboratory findings rule out electrolyte and glucose disturbances or hypoxemia as a cause of the observed encephalopathy.

(9) Elevated CO-Hb levels in a nonsmoker, in the absence of exogenous carbon monoxide exposure, is strongly suggestive of exposure to methylene chloride. A methylene chloride blood level, when available, can be used to confirm the presence of the chemical. Methylene chloride is mildly toxic to the liver. Liver function tests should be performed and could be used to rule out liver failure as a cause of dementia. Normal cardiac enzymes and serial ECGs indicate the patient did not have a myocardial infarction.

(10) There is no antidote or specific treatment for methylene chloride intoxication per se. The administration of oxygen will increase the dissociation of carbon monoxide from hemoglobin and thereby hasten the elimination of CO-Hb. Oxygen will also alleviate the tissue hypoxia.

(11) Most persons will recover from the acute and subacute effects of organic solvents on the central nervous system. Assuming there is no hypoxic tissue damage, your patient should also recover completely. Persons with long-term chronic exposure, such as painters and solvent abusers, may experience permanent neurobehavioral dysfunction, specifically, memory deficits and vestibular or cerebellar damage.

Paint-Remover Hazard

Richard D. Stewart, MD, MPH, Carl L. Hake, PhD

• The in-home use of paint removers containing methylene chloride results in the absorption of this solvent, which is metabolized to carbon monoxide. Exposure for two to three hours can result in the elevation of carboxyhemoglobin (COHb) to levels that stress the cardiovascular system. The metabolic formation of COHb continues following the paint-remover exposure, doubling the duration of the cardiovascular stress produced by a comparable COHb level after exposure to CO. Patients with diseased cardiovascular systems may not be able to tolerate this unexpected stress.

(*JAMA* 235:398-401, 1976)

THE REMOVAL of old paint from wood by applying a liquid paint stripping formulation, long regarded as a laborious, messy task, has not been considered particularly hazardous to health. However, recent research has shown that the main ingredient in most paint removers, methylene chloride (dichloromethane, CH_2Cl_2), is rapidly metabolized to carbon monoxide.[1-6] The amount of CO formed in the body is directly related to the amount of CH_2Cl_2 absorbed during the paint stripping operation and can be sufficient to produce a substantial stress on the cardiovascular system.

The first case illustrates the tragedy that can occur when a patient with coronary heart disease is exposed to a paint and varnish remover containing CH_2Cl_2 and the solvent is metabolized to a toxic amount of CO. The second case is the one in which the in vivo metabolism of CH_2Cl_2 to CO was first observed.

REPORT OF CASES

CASE 1.—A 66-year-old man with no prior history of heart disease was admitted to the coronary care unit with severe, crushing retrosternal pain of two hours' duration that radiated to his shoulder and left arm. The patient was a recently retired executive who had chosen furniture refinishing as a hobby. Six hours prior to admission he had applied a commercial liquid gel paint and varnish remover to part of a large wooden chest of drawers. He had worked at this task for three hours in his basement workshop, which was a room measuring 10.7×6.1×2.7 meters and was heated with hot air from a gas furnace. One hour after leaving the basement, he experienced the onset of his chest pain.

The patient related the history of the paint stripping to the attending physician who examined the paint and varnish remover container. The label cautioned that the product contained 80% methylene chloride by weight and was to be used only with adequate ventilation. No causal relationship between the inhalation of the paint remover vapor and the acute anterior myocardial infarction was made.

The patient had an uncomplicated hospital course, and two weeks following discharge he elected to strip the remaining paint from the chest of drawers. He again applied the paint remover, working for three hours in his basement workshop. The severe retrosternal pain developed again, and he was readmitted to the coronary care unit. His hospital course during this second acute myocardial infarction was complicated by cardiogenic shock, dysrhythmia, and heart failure. The patient survived, and six months after discharge returned once again to his basement workshop to complete the paint stripping operation. Assisted by his wife, he worked slowly for two hours. Two hours later he experienced chest pain, collapsed, and died before the arrival of the ambulance.

CASE 2.—A 35-year-old male cardiologist, who was enjoying excellent health, volunteered to participate in a research project, the purpose of which was to correlate the subject's carboxyhemoglobin (COHb) level

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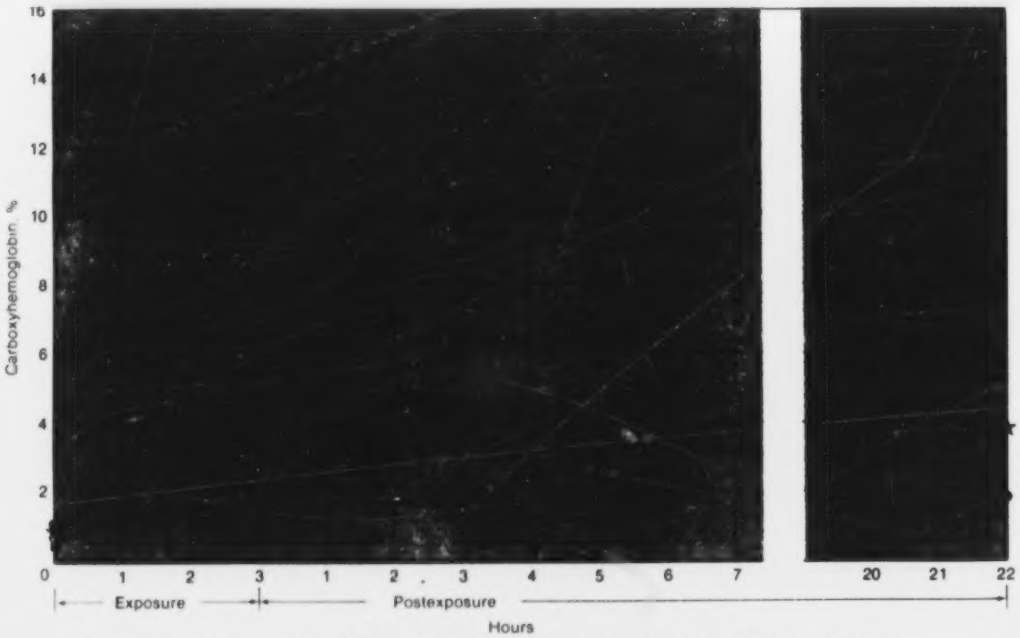

Short exposures to methylene chloride result in formation of carboxyhemoglobin (COHb) that continues to increase after exposure before slowly returning to normal levels. The presence of methanol further prolongs period of COHb elevation and cardiovascular stress.

with the air pollution in his section of Milwaukee. This nonsmoker was discovered to have a COHb saturation of 6%, and of 8% on each of the two mornings following a two-hour exposure the previous evening to paint-and-varnish-remover vapors. After a fruitless search to discover the exogenous source of CO, the cardiologist was exposed for one hour to a low concentration of methylene chloride vapor in a controlled-environment chamber.[3] The subject's COHb level rose from a preexposure level of 0.4% to 2.4%. Because there was no evidence of a hemolytic process, it was presumed that the CO was a metabolite of CH_2Cl_2. To confirm this isolated observation, a series of experiments were conducted in which 21 male and nine female volunteers were exposed to CH_2Cl_2 vapor concentrations of 50, 100, 250, 500, and 1,000 ppm for varying periods of time. A prompt elevation of COHb was observed in each subject exposed to CH_2Cl_2.[4,5]

EXPERIMENTAL PROCEDURE

Paint Remover Exposure.—To investigate the potential of paint and varnish removers that contain CH_2Cl_2 to elevate COHb to toxic levels, four three-hour paint stripping operations were carried out in a controlled-environment chamber where the ventilation rate could be regulated, the CH_2Cl_2 vapor concentration accurately monitored, and careful medical surveillance of the four volunteer participants was possible. Two individuals participated in each experiment. One actively applied the paint remover and did the stripping while the second subject remained sedentary, making it possible to assess the effect of alveolar ventilation on absorption. Three room-ventilation rates were studied. The first simulated the air turnover commonly encountered in home basements, while the other two simulated the higher rates of air turnover that could be encountered in industrial settings. In each three-hour experiment, one quart of a liquid gel paint remover was applied to a baby crib with a paint brush and later, scraped off. The volatile components of the paint remover were 80% CH_2Cl_2 and 20% methanol by weight.

Subjects.—Four healthy men ranging in age from 19 to 47 years volunteered for the study after the purpose, procedure, and risks of the investigation had been fully explained. None of the subjects used drugs or consumed alcohol during the 24-hour periods preceding and following each experiment. One subject, who was a smoker, abstained for 12 hours prior to the experiment and was not permitted to smoke until a final COHb determination had been made.

Exposure Chamber.—The four experiments were conducted in an 817-cu m (2,680-cu ft) controlled-environment chamber.[3-7] Air flow was adjusted so that the half-life of the CH_2Cl_2 vapor would range from 33 to 11 minutes. Air temperature was 22.3 to 23.3 C and the relative humidity was 55%.

Analysis of Exposure Chamber Atmosphere.—The CH_2Cl_2 vapor concentration in the breathing zone of the subjects was continuously recorded by an infrared spectrometer equipped with a 10-meter path-length gas cell. This gas cell was continuously supplied with air drawn from the subject's breathing zone through a polyethylene tubing that measured 0.635 cm in diameter.[3-7] The absorbance of 13.3μ

Table 1.—Concentration of Solvents in Breathing Zone During Paint Stripping

Experiment	Ventilation Rate, cu m/hr*	Breathing Zone CH_2Cl_2 Concentration, ppm			Breathing Zone Methanol Concentration, ppm
		Mean	Range	SD	
1	70.28	788	0-1277	354	. . .
2	70.28	654	0-1278	358	186
3	210.84	368	0-576	122	115
4	147.11	216	0-379	101	77

*Chamber Volume=75 cu m (2,680 cu ft).

Table 2.—Carboxyhemoglobin Levels During and Following Paint-Remover Exposure

Subject	Exposure Hours				Hours Postexposure							
	0	1	2	3	½	1	2	3	4	5	20	22.
Experiment 1*												
1	0.8	2.6	3.6	4.6	5.3	5.7	7.2	8.2	9.1	9.0	4.4	3.8
2	1.0	2.0	2.8	4.4	4.6	5.2	5.5	5.8	6.0	5.6	2.0	1.8
Experiment 2*												
3	1.0	2.3	3.3	4.0	. . .	5.2	6.1	6.7	6.9	6.5	3.0	2.5 (21 hr post)
4	2.2	2.8	3.8	4.1	. . .	5.0	5.5	5.9	5.9	5.5	3.0	2.6 (21 hr post)
Experiment 3 (forced ventilation [11.1 min to turn over 50% of air])												
1	0.9	2.8	4.0	4.8	6.0	6.8	7.3	6.5	3.1	2.9		
2	1.3	2.3	3.4	4.3	5.5	5.8	5.5	4.8	1.9	1.5		
Experiment 4 (forced ventilation [15.3 min to turn over 50% of air])												
3	0.9	1.2	1.9	2.9	3.4	3.4	3.3	3.2	1.8	1.6		
4	1.5	2.0	2.7	3.7	4.3	4.3	3.7	3.5	1.5	1.6		

*Normal home-basement ventilation (33 min to turn over 50% of air).

through a path length of 2.25 meters was measured. The infrared signal to the recorder was monitored each second by an on-line computer that displayed the mean vapor concentration, as compared to standards for each 30-second interval of exposure, and calculated the time-weighted average exposures. During the final five minutes of each hour of exposure, additional breathing zone samples were collected in large saran bags for methanol analysis.

Medical Surveillance.—Each subject was given a medical examination prior to exposure. This examination included a history, physical examination, and the following laboratory studies: complete blood cell count, 18-factor automated chemical analysis survey panel, and a 12-lead electrocardiogram. Prior to each day's exposure, the subjects were given a repeat medical examination. During exposure, the subjects were under continual surveillance by a physician, and lead II of each subject's ECG was continuously monitored by means of telemetry. Serial venous blood samples were obtained for COHb determination during and after the use of the paint remover (Figure).[8] The 18-factor automated chemical analysis and 12-lead electrocardiogram were repeated the morning following each exposure.

RESULTS

The use of the paint-remover formulation under the three ventilation rates produced the breathing zone CH_2Cl_2 and methanol concentrations listed in Table 1. The higher ventilation rates significantly reduced the breathing zone concentrations of the two solvents.

Each subject's COHb level began to increase shortly after exposure had begun (Figure). These COHb levels steadily increased during the exposure, continued to rise for several hours following cessation of exposure, and then very slowly returned to normal (Table 2). The more active volunteer in each experiment absorbed larger quantities of CH_2Cl_2, which resulted in higher COHb levels.

In contrast to the usual pattern of COHb formation following CH_2Cl_2 exposure, with peak COHb level elevations occurring one hour after exposure, the COHb level in those exposed to paint-remover vapors continued to increase for several hours following exposure. This suggested that the methanol was altering the usual metabolic degradation of CH_2Cl_2.

No untoward responses occurred during the 24-hour period following each exposure. None of the four subjects found the paint-remover vapors to be irritating to their eyes, nose, or throat. All described the odor as mild and not objectionable. No abnormalities in the ECGs or blood chemical values were recorded.

COMMENT

The use of a paint remover containing CH_2Cl_2 in a large interior room results in the absorption of a significant amount of solvent, its prompt metabolism to CO, and an elevation of blood COHb level. The greater the minute-respiratory volume or the poorer the room ventilation, the greater the absorption of CH_2Cl_2 and the higher the COHb level elevation. Use of the paint remover for a period of three hours, following the directions on the label, can easily produce a COHb saturation of 5% to 10%. Exposure for periods longer than those investigated or under conditions of poorer ventilation would result in even higher COHb elevations.

It has been well documented that elevation of COHb level to saturations greater than 5% can adversely affect patients with angina pectoris or cardiovascular disease.[9-12] Exercise tolerance is decreased and anginal pain is of longer duration. Yet paint stripping for furniture refinishing purposes has become extremely popular with older persons.[13] Until recently, a prominent Milwaukee hospital introduced paint stripping and furniture refinishing to coronary vein bypass patients in the early convalescent period.

The COHb resulting from the metabolism of CH_2Cl_2 is additive to the COHb level resulting from exposure to other exogenous sources of CO.[7] For example, a paint-remover exposure that results in a 10% COHb saturation level when added to a heavy smoker's preexisting COHb level of 10% will produce headache and nausea in the healthy, and sufficient cardiovascular stress in the patient with coronary heart disease to be dangerous.[9-12]

The elevated COHb level resulting from CH_2Cl_2 exposure has a biological half-life twice that of COHb produced from exposure to CO. This occurs because the absorbed CH_2Cl_2 is released slowly from storage in body tissues and then is metabolized to CO over a protracted period of time. Thus, because it is so sustained following exposure, the cardiovascular stress produced by elevated COHb levels, derived from CH_2Cl_2 metabolism, is greater than that resulting from equally high COHb levels derived from CO. The addition of methanol to paint-remover formulations extends the biologic half-life of COHb derived from CH_2Cl_2 (Figure), further prolonging the period of cardiovascular stress.

The ethical responsibility for informing the public about the potential hazard of CH_2Cl_2 in paint removers lies with the manufacturer who is obliged to market a product that can be used safely. This is the purpose of the label. It should warn the susceptible segment of the population of the CO hazard. The manufacturers of paint removers have been cognizant of the problem since 1972, yet product labels make no mention of CO. Only one manufacturer of paint removers has acted positively. This Racine, Wis, firm has withdrawn its product from the market.

The legal responsibility for protecting the public currently rests with the Consumer Product Safety Commission. It has remained mute, as did the governmental agency originally responsible, the Environmental Protection Agency, when in 1971 the CH_2Cl_2 hazard was formally called to its attention.

The medical responsibility for protecting patients unable to tolerate the cardiovascular stress of elevated COHb levels must rest with the physician until the general public is made aware of the CH_2Cl_2 hazard and all paint-remover formulations are appropriately labeled. This is a critical duty because one sixth of the 180 million kg of CH_2Cl_2 produced in the United States is being consumed in the rapidly expanding paint-remover market.[13]

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Anthony Wu, PhD, and Sally A. Graff provided technical assistance.

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Case Report

Fatal Outcome of Methemoglobinemia in an Infant

Carl J Johnson, MD; Pamela A Bonrud, MS; Terrance L Dosch; Arthur W Kilness, MD;
Kenneth A Senger; Darron C Busch; Michael R Meyer, MS

CASES of methemoglobinemia in infants and older members of farm families are probably more common than we realize. A 1950 report lists 144 cases of infant methemoglobinemia with 14 deaths in one 30-month period alone in Minnesota.[1] In a 1982 survey of 353 physicians in the ten-county Big Sioux region in eastern South Dakota, 29 physicians reported having treated about 80 cases of methemoglobinemia, of which 64 had occurred more than ten years earlier.[2] All but one case occurred in infants. This preventable, treatable intoxication continues to contribute to infant mortality today.

Report of a Case

A female infant born on April 30, 1986, was breast-fed at first and later received supplementary feedings with a powdered formula mixed with well water. The mother took her to the family physician for a one-month checkup on May 30. At that time, she looked quite healthy, although the mother reported blueness around the infant's mouth and of the feet and hands after about 2 weeks of age. This discoloration would come and go. The mother also noted that her daughter had experienced some trouble in breathing and had occasional diarrhea and vomiting. The blueness was attributed by her physician to changes in room temperature.

On June 21, 1986, the mother visited a pharmacy with the infant. The pharmacist commented that it looked as if the infant was not getting enough oxygen. The infant was given progressively larger amounts of the powdered infant formula prepared with well water. One week later (June 28), the infant began to vomit and had severe diarrhea and severe cyanosis. The parents rushed her to their physician who gave her oxygen for about 15 minutes. However, the infant's color did not improve. The physician noticed a heart murmur and referred the family to a hospital in another town 33 miles distant for further treatment. The infant stopped breathing during the trip. She was given cardiopulmonary resuscitation after arrival at the hospital but could not be resuscitated. The infant's blood was noted to be chocolate-brown. The well water at the farm was subsequently found to have a concentration of about 150 mg/L (150 parts per million [ppm]) of nitrate as nitrogen.

Comment

Background.—In rural states, such as South Dakota, Minnesota, Nebraska, and Iowa, a large proportion of the population relies on water from individual wells. In 1980, there were 56 512 domestic wells in use in South Dakota, providing water to 131 700 people. About 66% of these were farm wells.[3] There are special problems with the safety of well water for drinking due to poor construction and/or improper location, which may permit infiltration of surface waters contaminated with nitrates as well as other chemicals or microorganisms. (This is especially true of shallow wells, which easily become contaminated during periods of flooding, when runoff may contain chemical fertilizers from nearby cultivated fields. Similar problems can also occur following a heavy rainfall in drought-stricken areas.) A 1981 survey of more than 1000 wells in the Big Sioux river basin found that 27% of the wells had greater concentrations of nitrate in the water than permitted by the Environmental Protection Agency (EPA) (10 ppm or 10 mg/L of nitrate as nitrogen).[4] About 30% of the wells were contaminated with coliform bacteria.

Wells are most often contaminated by nearby feed lots, barnyards, or septic tank systems. In one study, 39% of dug or bored wells were unsafe due to high nitrate content, and 44% were unsafe due to contamination with coliform bacteria. Corresponding data for drilled wells were 22% and 26%; for driven wells, 16% and 8% were unsafe. Properly constructed wells more than 30 m (100 ft) deep are more likely to be safe.[5] Average concentrations of nitrates were 25 ppm in the dug or bored wells, 12 ppm in the drilled wells, and 7 ppm in the driven wells. In a recent review by D. Miller of the South Dakota Department of Water and Natural Resources (written communication, Dec 13, 1984) of more than 1000 well water samples sent for testing, 4% of the samples had concentrations greater than 100 ppm, 9% were greater than 50 ppm, 17% were greater than 20 ppm, and 27% exceeded 10 ppm, the EPA maximum contaminant level (samples were probably repeated for some wells). A comprehensive survey of individual well water quality in South Dakota has not been done.

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Although persons at any age may be affected by methemoglobinemia, infants are particularly susceptible during the first four months of life.[6] Newborn infants normally have a low concentration of methemoglobin reductase (erythrocyte cytochrome 5β-reductase), an enzyme that reduces methemoglobin. This concentration remains low until after 4 months of age.[6]

Infants who are breast-fed may possibly get some nitrite or nitrate in breast milk, but poisoning usually occurs when infant formula and other infant foods are prepared with contaminated water. Boiling the well water merely concentrates the nitrate. Nitrates do not directly reduce hemoglobin to methemoglobin but can be converted by intestinal microflora to nitrite, which can produce methemoglobinemia.[6] Aniline dyes may be absorbed through the skin and also cause methemoglobinemia.[6] Other chemical agents that cause methemoglobinemia include naphthalene and menadione (vitamin K_3). Chronic effects of subclinical levels of methemoglobinemia on growth, development, and general health apparently have not been studied.

Diagnosis.—When an infant is severely cyanotic with a relative absence of distress, methemoglobinemia should be suspected. These infants have a peculiar lavender color.[7] Blood from the heel stick is chocolate-brown and does not become pink when exposed to room air. Diagnosis can be confirmed by excluding other causes of cyanosis and by spectrophotometric analysis of blood for methemoglobin, which has a characteristic absorption peak at 634 μm. When methemoglobinemia levels reach 60% or greater, the patient will collapse and become comatose and may die.[6]

Treatment.—Patients who are only mildly affected do not require treatment, other than to avoid the contaminated source.[6] The methemoglobin levels will be reduced spontaneously over a period of two or three days. A severely affected patient requires therapy with methylene blue.[6,7] It may be sufficient to give 1 to 2 mg/kg of body weight of a 1% solution of methylene blue in saline intravenously over a ten-minute period. This converts the methemoglobin to hemoglobin and usually results in prompt relief of distress. If there is not an adequate response within an hour, a second dose can be administered. After the intravenous administration of methylene blue, it can be followed by 3 to 5 mg/kg of methylene blue orally or 200 to 500 mg of ascorbic acid orally.[7]

Prevention.—Because the consumption of well water with chemical or bacterial contamination may have serious consequences, especially for pregnant women and infants, physicians and community health nurses should be alert to this problem. Such wells should be tested annually to ensure their safety, especially before a new mother returns home with her infant. Further, the quality of well water may deteriorate overnight or change because of drought, a heavy rainstorm, flash flooding, spring thaw, or an application of pesticide or chemical fertilizer in a nearby cultivated field. Special precautions should be taken to ensure the safety of infants or persons in frail health. Public health nurses may make home visits to discuss infant feeding and preparation of formula and the use of well water. Alternative sources of water include water drawn from another well, which has tested safe; bottled water; a new deep well; water passed through a treatment device*; or connecting to a rural water system, if this is available.

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*Simple in-line filters are not effective for removing nitrates. Deionization, desalination, or reverse osmosis units are available, which *do* render water safe from nitrate contamination.

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ATSDR October 1991

Case Studies in Environmental Medicine

16

Nitrate/Nitrite Toxicity

Environmental ALERT . . .

- ☑ ***Nitrate toxicity causes methemoglobinemia, which is a wholly preventable disease.***
- ☑ ***Infants less than 4 months of age are at particular risk of nitrate toxicity from contaminated water.***
- ☑ ***The widespread use of nitrate fertilizers increases the risk of well-water contamination in rural areas.***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. See page 21 for more information about continuing medical education credits and continuing education units.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

A 2-month-old infant with vomiting, diarrhea, tachypnea, and cyanosis

A 2-month-old female infant is brought to your clinic in a rural area for a routine well-baby checkup. According to the child's chart, she was delivered 2 weeks early because of maternal toxemia. There was no neonatal distress; her birth weight was 7 pounds and 11 ounces.

Today, the mother states that she has noticed an intermittent bluish discoloration of the baby's lips, tip of the nose, and ears. Physical examination of the infant is negative for both cardiac murmurs and abnormalities on lung auscultation. A below-average weight gain is noted. Feedings have been 4 ounces of diluted formula every 2 hours. The infant has occasional loose stools. You instruct the parents to increase caloric feedings with vitamin and mineral supplements and to call you immediately if any further episodes of the bluish discoloration are observed.

Approximately 3 weeks later, the baby's frantic parents call your office; the infant is crying incessantly and has vomiting and profuse diarrhea. When the baby is brought to your clinic a few minutes later, she is afebrile but has tachypnea, cyanosis, and drowsiness. Her blood pressure is 78/30 mm Hg (normal 50th percentile for her age is 80/46 mm Hg), heart rate is 140/min, and respiration rate is 40/min. An ambulance is summoned and 100% oxygen by face mask is administered; however, no improvement in the cyanosis is noted on her arrival at the hospital emergency department.

The examining emergency physician now notes a grade II/VI systolic murmur and central cyanosis, which has not improved despite administration of 100% oxygen for nearly 1 hour. There is no evidence of cardiac failure, atelectasis, pneumonitis, or pneumothorax. Therapy is started, which results in a dramatic resolution of the cyanosis. The infant is discharged on the second hospital day with no evidence of central nervous system hypoxic damage.

Pretest

(a) *What was the most likely cause of this infant's cyanosis?*

(b) *What laboratory tests, either obtained during the hospitalization or ordered subsequently, would assist in confirming the diagnosis?*

(c) *What steps, if any, can be taken to prevent a recurrence of cyanosis and distress in this infant?*

Answers can be found on page 18.

Exposure Pathways

- ☐ **Shallow, rural domestic wells are most likely to be contaminated with nitrates, especially in areas where nitrogen-based fertilizers are in widespread use.**
- ☐ **Other nitrate sources in well water include seepage from septic sewer systems.**
- ☐ **Foodstuffs contaminated with nitrites and sausage preserved with nitrates and nitrites have caused symptomatic methemoglobinemia in children.**
- ☐ **Deliberate abuse of volatile nitrite inhalants can cause severe methemoglobinemia and death.**

Nitrate (NO_3^-) and nitrite (NO_2^-) are naturally occurring inorganic ions, which are part of the nitrogen cycle. Wastes containing organic nitrogen are decomposed in soil or water by microbial action to first form ammonia, which is then oxidized to nitrite and nitrate. Because nitrite is easily oxidized to nitrate, it is nitrate that is predominantly found in groundwater and surface waters. Contamination with nitrogen-containing fertilizers, including anhydrous ammonia as well as animal or human natural organic wastes, can raise the concentration of nitrate in water. Nitrate-containing compounds in the soil are generally soluble and readily migrate with groundwater.

In agricultural areas, nitrogen-based fertilizers are a major source of contamination for shallow groundwater aquifers that provide drinking water. A 1990 Environmental Protection Agency (EPA) survey found that about 1.2% of community wells and about 2.4% of rural domestic wells had nitrate concentrations in excess of federal regulatory limits. (see page 15) A similar survey conducted in Iowa indicated that about 18.3% of rural domestic wells contained concentrations of nitrate above the regulatory level. Other sources of nitrate contamination are organic animal wastes and contamination from septic sewer systems, especially in wells less than 100 feet deep. During spring melt or drought conditions, both domestic wells and public water systems using surface water may have increased nitrate concentrations.

Although vegetables are seldom a source of acute toxicity, they account for more than 70% of the nitrates in a typical human diet. Cauliflower, spinach, collard greens, broccoli, and root vegetables have a naturally greater nitrate content than other plant foods. The remainder of the nitrate in a typical diet comes from drinking water (about 21%) and from meat and meat products (about 6%) in which sodium nitrate is used as a preservative and color-enhancing agent.

Symptomatic methemoglobinemia has occurred in children who have eaten sausage heavily treated with nitrates and nitrites. For infants, the major source of nitrate exposure is drinking water used to dilute formula.

Accidental exposure to nitrites in chemical laboratories and ingestion in suicide attempts have been described. Deliberate abuse of volatile nitrites (amyl, butyl, and isobutyl nitrites) as psychedelics or aphrodisiacs occurs widely; these agents are known by street names such as "snappers," "poppers," "Locker Room," and "Rush."

Nitrate or nitrite exposure also may occur from certain medications. Infants and children are especially susceptible to nitrate exposure through topical silver nitrate used in burn therapy. Other medications implicated in cases of nitrate or nitrite toxicity are quinone derivatives (antimalarials), nitroglycerine, bismuth subnitrite (antidiarrheal), ammonium nitrate (diuretic), amyl and sodium nitrites (antidotes for cyanide and hydrogen sulfide poisoning), and isosorbide dinitrate/tetranitrates (vasodilators used in coronary artery disease therapy). (See Table 1.)

Sodium nitrite used as an anticorrosive agent in cooling fluids, ammonium nitrate found in cold packs, and nitrous gases used in arc welding are other possible sources of exposure. An ethyl nitrite folk remedy called "sweet spirits of nitre" has caused fatalities. Serious poisoning and death have occurred when sodium nitrate was mistaken for table salt and ingested with food.

Table 1. Reported inducers of methemoglobinemia

AGENT	SOURCE/USE
Inorganic nitrates/nitrites	Contaminated well water Meat preservatives Vegetables—carrot juice; spinach Silver nitrate burn therapy Industrial salts Contaminants of nitrous oxide canisters for anesthesia
Organic nitrites	
Butyl/isobutyl nitrite	Room deodorizer propellants
Amyl nitrite	Inhalant in cyanide antidote kit
Nitroglycerine	Oral, sublingual, or transdermal pharmaceuticals for treatment of angina
Others	
Aniline/aminophenols	Laundry ink
Nitrobenzene	Industrial solvents; gun-cleaning products
Local anesthetics	Benzocaine; lidocaine; Propitocaine®; Prilocaine®
Sulfonamides	Antibacterial drugs
Phenazopyridine	Pyridium®
Antimalarials	Chloroquine®; Primaquine®
Sulfones	Dapsone®
p-Aminosalicylic acid	Bactericide (tuberculostatic)
Naphthalene	Mothballs
Copper sulfate	Fungicide for plants, seed treatment
Resorcinol	Antiseborrheic, antipruritic, antiseptic
Chlorates	Matches, explosives, pyrotechnics
Combustion products	Fires

Adapted from: Dabney BJ, Zelarney PT, Hall AH. Evaluation and treatment of patients exposed to systemic asphyxiants. Emergency Care Quarterly 1990;6(3):65-80

Challenge

(1) What questions will you ask the parents of the infant in the case study to help determine the cause of the cyanosis?

(2) If well water used to dilute formula is implicated in the cyanosis, what are some possible causes of its nitrate contamination?

Who's at Risk

- ☐ **Infants less than 4 months of age are at the greatest risk for nitrate toxicity.**
- ☐ **About 1% to 2% of the U.S. population that uses drinking water from public water systems may be exposed to nitrates in excess of the EPA-recommended maximum concentration.**

Infants less than 4 months of age who are fed formula diluted with water from rural domestic wells are especially prone to developing acute acquired methemoglobinemia from nitrate exposure. The pH of the gut is normally higher in infants than in older children and adults. Higher gut pH enhances the conversion of ingested nitrate to more potent nitrite; gastroenteritis with vomiting and diarrhea can exacerbate nitrite formation.

A large proportion of hemoglobin in infants is in the fetal hemoglobin form, which is more readily oxidized by nitrites to methemoglobin than adult hemoglobin is. In infants, NADH[*]-dependent methemoglobin reductase, the enzyme responsible for reduction of methemoglobin back to normal hemoglobin, has only about half the activity present in adults. These factors combine to place young infants who are fed formula diluted with nitrate-contaminated well water at the greatest risk of toxicity. There is little evidence that breast-fed infants develop methemoglobinemia from exposure to nitrates ingested by the nursing mother.

[*] Reduced form of nicotinimide adenine dinucleotide

The first reported case of fatal acquired methemoglobinemia in an infant due to ingestion of nitrate-contaminated well water occurred in 1945. Since that time about 2,000 similar cases of acquired methemoglobinemia in young infants have been reported worldwide; about 10% of such cases result in fatality. The most recently reported U.S. case of infant mortality due to this source was in 1987.

In pregnant women, the level of methemoglobin increases from the normal (0.5% to 2.5% of total hemoglobin) to a maximum of 10.5% at the 30th week of pregnancy and subsequently declines to normal after delivery. Thus, pregnant women may be more sensitive to the induction of clinical methemoglobinemia by nitrites or nitrates at or near the 30th week of pregnancy.

It has been estimated that 1% to 2% of the U.S. population using drinking water from public water systems may be consuming nitrates in excess of the EPA-recommended maximum concentration. It has also been estimated that residents in as many as 603,000 homes consume drinking water from nitrate-contaminated domestic wells. Although suppliers of public water sources are required to monitor nitrate concentrations regularly, rural wells often are not routinely tested for nitrates.

Challenge

(3) What recommendations can you make to the infant's family in the case study to prevent further cyanotic episodes?

Biologic Fate

- ☐ **In vivo conversion of nitrates to nitrites significantly enhances nitrates' methemoglobin-inducing potency.**
- ☐ **Nitrates are excreted rapidly in the urine.**

In humans, ingested nitrate is rapidly absorbed from the proximal small bowel and distributed throughout the body. Nitrate then enters the large bowel from the blood, where it is rapidly converted to highly reactive nitrite, in part by fecal microorganisms. The formed nitrite is reabsorbed into the blood, where it reacts with the ferrous (Fe^{2+}) iron of deoxyhemoglobin, forming methemoglobin with iron in the ferric (Fe^{3+}) valence state. Ferric iron is unable to transport oxygen.

Nitrates are rapidly converted in the liver to denitrated metabolites and inorganic nitrites, which are then excreted in urine. Approximately 60% to 70% of an ingested nitrate dose is excreted in urine within the first 24 hours. About 25% is excreted in saliva through an active blood nitrate transport system and potentially is reabsorbed. Half-lives of parent nitrate compounds are usually less than 1 hour; half-lives of metabolites range from 1 to 8 hours.

Challenge

(4) What factors make infants less than 4 months of age more susceptible to developing methemoglobinemia when exposed to nitrates?

Physiologic Effects

Unless favorable conditions exist for reducing nitrate to nitrite in the gut (i.e., high pH, proper intestinal microbial flora), ingested nitrate (NO_3^-) is metabolized and excreted without producing apparent adverse effects. The effects of nitrite (NO_2^-) are the same whether nitrite-containing compounds are ingested or inhaled, or nitrite is produced in vivo from nitrate.

Hematologic Effects

The principal mechanism of nitrite toxicity is the oxidation of the ferrous iron (Fe^{2+}) in deoxyhemoglobin to the ferric (Fe^{3+}) valence state, producing methemoglobin. Methemoglobin cannot reversibly bind or transport circulating oxygen. Depending on the percentage of total methemoglobin in oxidized form, the clinical picture is one of oxygen deprivation with cyanosis, cardiac dysrythmias and circulatory failure, and progressive central nervous system (CNS) effects. The CNS effects may range from mild dizziness and lethargy to coma and convulsions.

☐ **Acute acquired methemoglobinemia is the most important adverse health effect caused by excessive nitrate exposure.**

☐ **Some methemoglobin-inducing agents can also cause Heinz body hemolytic anemia or sulfhemoglobinemia.**

Hemoglobin protein may also be oxidized, causing denaturation and erythrocyte hemolysis and resulting in hemolytic anemia. The denatured protein is visible on special peripheral blood stains as Heinz bodies (minute bodies sometimes seen in erythrocytes by the dark illumination method). Many agents that induce methemoglobin can also induce a sulfhemoglobinemia, which is usually benign but may confound the diagnosis. Sulfhemoglobin may produce cyanosis that is apparent at concentrations as low as 3% to 5% total hemoglobin.

Two enzymes (one NADH-dependent, the other NADPH-dependent) are normally present that reduce methemoglobin back to hemoglobin. A physiologic methemoglobinemia (1% to 2% of total hemoglobin) is typical in humans as a result of exposure to oxidizing substances and diet. A rare *congenital methemoglobinemia* (10% to 50% of total hemoglobin) may be found in persons with either hemoglobin M disease* or a deficiency of NADH-dependent methemoglobin reductase. *Acquired methemoglobinemia* is caused by exposure to oxidizing substances including nitrates and nitrites. Persons with a deficiency of NADH-dependent reductase may be more susceptible to developing symptomatic methemoglobinemia after exposure to nitrates and nitrites.

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* A disease caused by a group of abnormal hemoglobins in which a single amino acid substitution favors the formation of methemoglobin, in spite of normal quantities of methemoglobin reductase

Cardiovascular Effects

☐ **Hypotension, shock, and cardiac arrhythmias may occur in cases of severe methemoglobinemia.**

In large doses, nitrite is an excellent vasodilator due to its relaxing action on vascular smooth muscle; hypotension and shock can result. Systolic flow murmurs may be heard on auscultation in persons with severe methemoglobinemia, which may develop with too-rapid intravenous administration of sodium nitrite (used as an antidote for cyanide and hydrogen sulfide poisoning) or sodium nitroprusside (used in hypertensive crisis therapy). In patients who have inhaled volatile nitrites, transient electrocardiographic changes (T-wave inversions and ST-segment depression) may be noted.

Respiratory Effects

☐ **Severe methemoglobinemia may lead to metabolic acidosis.**

Metabolic acidosis develops in cases of severe methemoglobinemia, especially in young infants or when hypotension and shock are present. Dyspnea and tachypnea are common findings in patients with significant methemoglobinemia. Respiratory tract irritation may occur in patients who abuse volatile nitrites.

Other Effects

☐ **Chocolate-brown cyanosis is a hallmark of methemoglobinemia.**

A chocolate-brown or slate-gray central cyanosis (involving the trunk and proximal portions of the limbs, as well as the distal extremities and mucous membranes) is one of the hallmarks of methemoglobinemia. This cyanosis is due to the dark chocolate-brown color of methemoglobin itself and usually becomes noticeable at a concentration of 10% to 15% of total hemoglobin.

Concern has been expressed about the cancer-causing potential of nitrates and nitrites used as preservatives and color-enhancing agents in meats. Nitrates can react with amino acids to form nitrosamines, which have been reported to cause cancer in animals. However, data from human and experimental animal studies have failed to provide conclusive evidence that nitrate or nitrite ingestion causes carcinogenic or teratogenic effects.

Clinical Evaluation

History and Physical Examination

☐ **Cyanosis that fails to improve with administration of 100% oxygen is a sentinel finding in cases of methemoglobinemia.**

Evaluation of a patient with suspected nitrate/nitrite exposure includes a complete medical history and physical examination. Clues to potential exposure are often obtained by reviewing the following items with the patient or family:

- Location of dwelling (urban, suburban, rural)
- Drinking water source and supply (in case of well water: depth, location, type of well construction, and frequency of microbiologic and nitrate testing)
- Surrounding activities (agricultural, industrial) and proximity to drinking-water source
- Type of sewer system (municipal, septic) and proximity to drinking-water source
- Occupations, avocations, and hobbies of family members
- Nutritional status (for infants: type of formula, feeding regimen, and source of dilution water)
- Family history, including recent use of medications by infant and mother
- History of recent gastroenteritis with vomiting or diarrhea

Physical examination should include special attention to the color of the skin and mucous membranes. If a history of gastroenteritis is present (especially in infants), evaluate the patient for the possible presence of dehydration (poor skin turgor, sunken fontanelle, dry mucous membranes). All cyanotic patients should be assessed for possible cardiac and lung disease (cardiac murmurs, gallops, arrhythmias; rales, rhonchi, wheezes, dullness or hyperresonance in the chest). A central chocolate-brown or slate-gray cyanosis that does not respond to administration of 100% oxygen is indicative of methemoglobinemia; cyanosis due to cardiorespiratory compromise most often improves with administration of 100% oxygen.

In young infants, look for labored breathing, respiratory exhaustion, hypotension, below-average weight gain, and failure to meet developmental milestones. Gastroenteritis can increase the rates of production and absorption of nitrites in young infants and aggravate methemoglobinemia.

Signs and Symptoms

Signs and symptoms of methemoglobinemia can be directly correlated with the percentage of total hemoglobin in the oxidized form (Table 2).

☐ **Signs and symptoms of methemoglobinemia are related to the percentage of oxidized hemoglobin in the blood.**

Table 2. Signs and symptoms of methemoglobinemia

Methemoglobin concentration	Clinical findings
10%-20%	Central cyanosis of limbs/trunk; usually asymptomatic
20%-45%	CNS depression (headache, dizziness, fatigue, lethargy, syncope), dyspnea
45%-55%	Coma, arrhythmias, shock, convulsions
>70%	High risk of mortality

From: Dabney BJ, Zelarney PT, Hall AH. Evaluation and treatment of patients exposed to systemic asphyxiants. Emergency Care Quarterly 1990;6(3):65-80

The lips and mucous membranes of patients with nitrate/nitrite toxicity usually have more of a brownish than a bluish cast. Dyspnea, especially on exertion, is common. Varying degrees of central nervous system depression may be present. The cardiac and pulmonary examinations are usually normal, but systolic flow murmurs may be detected. Cardiac arrhythmias and hypotension may occur in patients with severe poisoning, although death from methemoglobinemia alone is uncommon, except in infants.

Laboratory Evaluation

Most commonly, a drop of the patient's blood is placed on a piece of filter paper alongside a drop of blood from a normal individual; when dry, the methemoglobin-containing blood will turn a deep chocolate-brown or slate-gray color in comparison. A tube of methemoglobin-containing blood will not turn red when shaken in air or when oxygen is bubbled through it; whereas blood that is dark because of a high content of normal deoxyhemoglobin will turn red.

☐ **Methemoglobinemia results in distinct changes in blood color and oxygen-carrying capacity.**

Screening Tests

- Examination of blood color
- Determination of the calculated versus measured arterial saturation gap
- Hemoglobin and hematocrit
- Serum-free hemoglobin (for hemolysis detection)
- Serum haptoglobin (for hemolysis detection)
- Heinz bodies on peripheral blood smear
- Urinalysis

Specialized Tests

- Determination of methemoglobin level
- Tests for causes of congenital methemoglobinemia:
  - Hemoglobin electrophoresis
  - Activity of NADH-dependent methemoglobin reductase
- Tests for causes of failure of methylene blue therapy (see Treatment and Management, page 13):
  - Activity of glucose-6-phosphate dehydrogenase (G-6-PD)
  - Activity of NADPH-dependent methemoglobin reductase
  - Sulfhemoglobin blood level (not readily available for clinical use)

Direct Biologic Indicators

☐ **Measurements of nitrates or nitrites in blood, urine, or saliva are not clinically useful.**

Although 80% to 90% of the body's excretion of nitrate is through urine and saliva, biologic nitrate or nitrite levels are generally not useful for diagnostic purposes. However, urinary and salivary nitrate concentrations can be important indicators of exposure requiring remedial action. The correlation between blood nitrite and methemoglobin is not usually linear at lower nitrite concentrations since a certain minimum amount of nitrite must enter the bloodstream before a measurable increase in methemoglobin concentration can be detected.

Indirect Biologic Indicators

☐ **The most useful diagnostic test for nitrate toxicity is a blood methemoglobin level.**

☐ **Percent O_2 saturation is an important but nonspecific finding in patients with methemoglobinemia.**

The methemoglobin level in blood is the most useful screening, as well as diagnostic, test for nitrate toxicity. Methemoglobin can be measured in whole blood using a visible spectrophotometer (or Co-Oximeter) at 635 nanometers. To express the methemoglobin level as a percentage, total hemoglobin content of the blood sample also must be determined. Oximeters used to measure methemoglobin levels may falsely report sulfhemoglobin as methemoglobin. Although sulfhemoglobinemia is seldom severe enough to be life-threatening, its presence can explain some methylene blue treatment (see Treatment and Management, page 13) failures. For the evaluation of suspected congenital methemoglobinemia, hemoglobin electrophoresis is helpful.

In patients with methemoglobinemia, the partial pressure of oxygen (pO_2) is usually normal despite the presence of an abnormal hemoglobin that cannot bind or transport oxygen. The percent O_2 saturation calculated by some blood-gas instruments from the pO_2, or calculated manually with a nomogram, will be normal. However, the percent O_2 saturation actually measured with a Co-Oximeter will be decreased, resulting in a calculated versus measured arterial "percent O_2 saturation gap." This finding is not specific for methemoglobinemia, however, since carboxyhemoglobinemia and sulfhemoglobinemia produce the same findings.

Percent O_2 saturation determined with a pulse oximeter may be unreliable in patients with methemoglobinemia, especially after administration of methylene blue (see Treatment and Management, page 13). Arterial blood gases should be used to monitor oxygenation in such patients.

Environmental Indicators

In young infants, drinking water is the most common source of nitrate exposure. Water tests for nitrate can be obtained from any public health laboratory that utilizes approved EPA procedures. Care should be taken to compare the results to the reference units provided by the laboratory. Some laboratories report nitrate levels as milligrams per liter (mg/L) nitrate; others report nitrate levels as mg/L nitrate-nitrogen (NO_3-N).

☐ **Since drinking water is the most common source of nitrates, testing the water supply of patients with a suspected exposure is prudent.**

Challenge

(5) In addition to methemoglobinemia, what other clinical conditions may occur from exposure to methemoglobin-inducing substances?

(6) What laboratory tests are useful for evaluating a patient with suspected methemoglobinemia?

Treatment and Management

- ☐ **Methylene blue is an effective antidote for most patients with methemoglobinemia.**
- ☐ **Treatment alone is insufficient; the nitrate source must be identified and eliminated from the patient's environment.**

In cases of mild nitrate toxicity (blood methemoglobin levels less than 20%), asymptomatic patients do not require treatment other than avoiding ingestion or inhalation of substances that cause methemoglobinemia. In symptomatic patients with moderate or severe toxicity and hypoxia or dyspnea, 100% oxygen should be administered immediately to fully saturate all remaining normal hemoglobin.

Specific therapy for methemoglobinemia consists of intravenous administration of methylene blue at a dose of 1 to 2 milligrams/kilograms (mg/kg) body weight (0.1 to 0.2 milliliters [mL]/kg body weight of a 1% solution in saline) over a 5-to10-minute period. Within 15 minutes of methylene blue administration, cyanosis will usually begin to improve obviously. If no response to the initial injection has occurred within 15 minutes in seriously ill patients, or within 30 to 60 minutes in moderately ill patients, a second methylene blue dose of 0.1 mL/kg body weight may be given. Caution is advised since methylene blue can slightly worsen methemoglobinemia when given in excessive amounts. In general, the total dose administered during the first 2 to 3 hours should not be greater than 0.5 to 0.7 mL/kg of body weight.

Methylene blue should not be administered to a patient with known G-6-PD deficiency, as severe hemolytic anemia may develop.

For severe, life-threatening methemoglobinemia, especially when the patient responds poorly to methylene blue therapy or when the patient is known to have G-6-PD deficiency, treatment options include exchange transfusion and hyperbaric oxygen therapy. During treatment in the hyperbaric chamber, sufficient oxygen can be dissolved directly in the blood to support life; reversible binding to hemoglobin is not required.

Blood transfusion may be required if massive hemolysis develops. In persons with severe hemolysis, maintaining a brisk urine flow and alkalinizing the urine by administration of sodium bicarbonate may help protect against renal injury from erythrocyte breakdown products.

Patients with severe poisoning who are experiencing seizures or cardiac arrhythmias may require anticonvulsant or antiarrhythmic therapy. If a local anesthetic is suspected of being the etiologic agent for the methemoglobinemia, however, lidocaine probably should be avoided.

Treatment alone is not adequate for nitrate poisoning. The patient and the nitrate source must be permanently separated. In the case of infantile acquired methemoglobinemia, well water used in preparing formula is a primary etiologic suspect. Physicians and community health personnel should be aware that high nitrate levels in water supplies may suggest the presence of bacterial contamination or agricultural chemicals, which might have serious consequences, especially for infants and pregnant women (increased methemoglobin sensitivity), as well as potential fetal risk. The conventional approach of boiling water to destroy microorganisms is not a safe practice when nitrate contamination is suspected; evaporation actually increases the nitrate concentration.

Alternative sources of uncontaminated water may include water from a well that has been tested and found to have an acceptable nitrate content, bottled water, water from a new and deeper well, or water from a regularly monitored public water supply. Water treatment technologies (ion exchange resins or reverse osmosis) to remove nitrate from water are not adequate to remove other associated contaminants, especially coliform bacteria. Private wells should be tested for nitrate concentration annually.

Challenge

(7) Why might some patients with methemoglobinemia not respond to treatment with methylene blue?

(8) What options are available to treat significant methemoglobinemia in a patient known to have G-6-PD deficiency?

Standards and Regulations

The nitrate limit in drinking water was established as a safeguard against infantile acquired methemoglobinemia. The EPA regulations require the nitrate content of potable water to be below 45 mg/L (45 parts per million [ppm]) measured as nitrate (NO_3^-) or 10 mg/L (10 ppm) measured as nitrogen in nitrate (NO_3-N).

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Sources of Information

More information on the adverse effects of nitrates/nitrites and treating and managing cases of exposure to nitrates/nitrites can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Nitrate/Nitrite Toxicity* is one of a series. For other publications in this series, please use the order form on the back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of the Director, at (404) 639-0730.

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Answers to Pretest and Challenge Questions

Pretest

Pretest questions are on page 1.

(a) In an infant, cyanosis that is unresponsive to oxygen therapy is most likely due to methemoglobinemia.

(b) The clinical laboratory tests that will confirm the diagnosis of methemoglobinemia are blood color and arterial blood gases. When a drop of methemoglobin-containing blood is placed on filter paper, it dries a deep chocolate-brown or slate-gray color. The level of methemoglobin in the blood can be measured using a Co-Oximeter. Analysis of arterial blood gases will reveal normal oxygen pressure.

In the case of infantile acquired methemoglobinemia, well water used to prepare formula should be tested for the presence of nitrates. Ingestion of nitrate-containing water is not an uncommon cause of methemoglobinemia in infants, especially those residing in rural areas.

(c) The initial step in preventing a recurrence of the infant's cyanosis and distress is to identify the cause of the infant's cyanosis; the next step is to correct or eliminate the cause. If the infant is suffering from acquired methemoglobinemia, the agent must be identified and removed from the infant's environment.

Challenge

Challenge questions begin on page 4.

(1) Questions that may help define the cause of the cyanosis include dwelling location; surrounding activities; type of sewer system; occupations, avocations, and hobbies of family members; drinking water source and supply; in infants, the type of formula, feeding regimen, and source of dilution water; family history, including recent use of all medications by both infant and mother; and in infants, a history of recent gastroenteritis.

(2) Causes of high nitrate concentrations in well water include runoff from the use of nitrogen-containing agricultural fertilizers (including anhydrous ammonia) and seepage of organic nitrogen-containing material from animal wastes or septic sewer systems.

(3) The well water should be tested for nitrate concentration and presence of coliform bacteria. It is most important to identify the source of the methemoglobin-inducing agent and to preclude any further exposure to the infant. If nitrate-contaminated well water is the source, utilizing bottled or other uncontaminated water to dilute formula should be recommended.

You could also recommend frequent testing of the well for nitrate concentration and bacterial contamination, or drilling a new and deeper well, taking into consideration the proximity of septic sewer systems, location of animal wastes, and proximity to agricultural land that may be regularly treated with nitrogen-based fertilizers.

(4) Infants less than 4 months of age are more susceptible to developing methemoglobinemia because the pH of the gut is normally higher than in older children and adults, which enhances the conversion of ingested nitrate to the more potent nitrite. The bacterial flora of the young infant's gut is also different from that found in older children and adults and may be more likely to convert ingested nitrate to nitrite. Gastroenteritis can increase both the in vivo transformation of nitrate to nitrite and the systemic absorption of nitrite from the large intestine.

A large proportion of hemoglobin in young infants is in the form of fetal hemoglobin. Fetal hemoglobin is more readily oxidized to methemoglobin by nitrites than is adult hemoglobin. Also, in infants, NADH-dependent methemoglobin reductase, the enzyme responsible for reduction of induced methemoglobin back to normal hemoglobin, has only about half the activity present in adults.

(5) Hemolytic anemia or sulfhemoglobinemia can be caused by many substances that induce methemoglobinemia.

(6) The level of methemoglobinemia can be measured with a Co-Oximeter. Although biologic nitrate and nitrite levels can be determined, these tests are not routinely performed; it is more expedient to identify and measure nitrate at its source (e.g., contaminated well water).

If congenital methemoglobinemia is suspected or if the patient responds poorly to treatment with methylene blue, the following tests should be performed: hemoglobin electrophoresis, G-6-PD activity, and the activities of NADH- and NADPH-dependent methemoglobin reductases.

(7) Some patients may not respond to methylene blue treatment because they have a G-6-PD deficiency, sulfhemoglobinemia, or hemoglobin M disease.

(8) Treatment options for patients with G-6-PD deficiency include exchange transfusion and hyperbaric oxygen therapy.

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An Outbreak of Nitrogen Dioxide–Induced Respiratory Illness Among Ice Hockey Players

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During February 1987 an outbreak of nitrogen dioxide–induced respiratory illness occurred among players and spectators of two high school hockey games played at an indoor ice arena in Minnesota. The source of the nitrogen dioxide was the malfunctioning engine of the ice resurfacer. Case patients experienced acute onset of cough, hemoptysis, and/or dyspnea during, or within 48 hours of attending, a hockey game. One hundred sixteen cases were identified among hockey players, cheerleaders, and band members who attended the two games. Members of two hockey teams had spirometry performed at 10 days and 2 months after exposure; no significant compromise in lung function was documented. Nitrogen dioxide exposure in indoor ice arenas may be more common than currently is recognized; only three states require routine monitoring of air quality in ice arenas, and the respiratory symptoms caused by exposure to nitrogen dioxide are nonspecific and easily misdiagnosed.

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NITROGEN dioxide is a brownish gas produced as a by-product of combustion. Occupational exposures to nitrogen dioxide are frequent among silo fillers, arc welders, firefighters, and workers who manufacture missile fuels and explosives.[1,2] The effects of nitrogen dioxide depend on the level and duration of exposure. Exposure to moderate levels (50 ppm) for brief periods may produce cough, hemoptysis, dyspnea, and chest pain.[3] Exposure to high concentrations of nitrogen dioxide (>100 ppm) can produce pulmonary edema, which can be acutely fatal or may lead to bronchiolitis obliterans.[4,5] Bronchiolitis obliterans may result in chronic restrictive pulmonary disease; however, most patients recover, with few long-term sequelae. Treatment with corticosteroids may diminish the severity of disease.[6,7] Exposure to low levels of nitrogen dioxide also may produce adverse pulmonary effects. Human volunteers exposed to 5 ppm of nitrogen dioxide for 15 minutes and 2.5 ppm for 2 hours demonstrated increased pulmonary airway resistance.[8] Also, recent studies suggest that long-term exposure to low levels of nitrogen dioxide, in the environment or in the home, may predispose residents to respiratory infections and chronic obstructive pulmonary disease.[9-13] The National Institute for Occupational Safety and Health recommends 1 ppm of nitrogen dioxide as a work-site standard.[1]

During February 1987, we investigated an outbreak of acute respiratory illness in participants and spectators of two high school hockey games played at an indoor ice arena located in a suburb of St Paul, Minn. The outbreak was caused by nitrogen dioxide gas emitted from the malfunctioning engine of the ice resurfacer, commonly referred to as a "Zamboni," named after its inventor (*Sports Illustrated*. March 30, 1987: 38-45). Because outbreaks of nitrogen dioxide–induced respiratory illness in this setting are reported rarely, our epidemiologic and clinical findings are presented herein.

BACKGROUND

On February 20, 1987, the Minnesota Department of Health, Minneapolis, was notified by a high school hockey coach that several members of two teams (A and B) experienced acute onset of cough, hemoptysis, and/or chest pain during or immediately after a game at an indoor ice arena on February 17, 1987. In addition, members of two hockey teams (C and D) that had played a game at the arena 5 days earlier (February 12, 1987) had developed similar symptoms during or shortly after their game at the arena. Three of the four hockey teams (A, B, and C) had played at the arena only one time; team D held daily practices and played weekly games at the arena.

The arena was community owned and operated. During practices, the ice was

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resurfaced for 10 minutes every hour; during games, the ice was resurfaced for 5 minutes after each 15-minute period. A Plexiglas shield surrounded the ice to protect spectators from airborne hockey pucks. Two ventilation systems were used in the arena: air vents for passive air exchange and exhaust fans.

The ice resurfacer was powered by an internal combustion engine using propane fuel. If these engines are not properly tuned and the fuel mixture in the carburetor receives too little oxygen, elevated levels of carbon monoxide may be produced; if the mixture has too much oxygen, elevated levels of nitrogen dioxide may be produced.[16]

Ice arenas in Minnesota are required to measure ambient levels of carbon monoxide and nitrogen dioxide on a weekly basis during the months of operation. Measurements are taken 120 cm above the ice in the center of the arena. Ambient levels of nitrogen dioxide above 0.5 ppm are considered to be elevated and are required to be reported to the Minnesota Department of Health.

METHODS

Epidemiologic and Clinical Investigation

Questionnaires were administered to all hockey team members who attended the two games. In addition, cheerleaders and band members, who were present during the second game, were interviewed. Information was obtained on symptoms (including cough, hemoptysis, shortness of breath, dyspnea, chest pain, headache, and weakness), onset and duration of each symptom, general health status (including history of asthma or other respiratory problems), length of time in the arena, and location in the arena during the games (in the stands or on the ice). For hockey players, information also was obtained on position played and length of time on the ice. All interviews were completed within 10 days after attending a game at the arena. A *case* was defined as acute onset of cough, hemoptysis, or dyspnea during a hockey game or within 48 hours of attending a hockey game at the arena. Attack rates for teams were compared using standard univariate analysis.[17]

Spirometry was performed within 10 days of exposure and again at 2 months after exposure for all members from two hockey teams: team C (with a single exposure) and team D (with multiple exposures). Spirometry also was performed on members of a basketball team from one of the schools, which served as an unexposed group for comparison. Pulmonary function testing was performed at the high schools that the players attended using a portable spirometer (Microloop, Medical Graphics Corp, St Paul, Minn). The best result of three attempts was recorded. Intermountain Thoracic Society predicted values (which control for age, height, and weight) were used to determine results by percent of predicted.[18]

We reviewed medical records for hockey players who reported seeing a physician. Information was obtained on physical examination, chest roentgenogram findings, and treatment prescribed during initial and follow-up clinic visits.

Environmental Investigation

Air quality records at the ice arena were reviewed for the hockey season. No measurements had been obtained during the two games in question. Therefore, to simulate conditions during the games, the ice resurfacer was operated for 30 minutes and levels of nitrogen dioxide and carbon monoxide in the arena were measured. The use of the ventilation systems during the two games also was reviewed.

Survey of State Health Departments

To evaluate air quality monitoring in indoor ice arenas nationally, and to obtain an estimate of the number of ice arenas located in each state, a telephone survey of all 50 state health departments was conducted. The Ice Skating Institute of America, the US Figure Skating Association, and the National Hockey Association also were contacted to obtain estimates of the number of indoor ice arenas located in the United States.

RESULTS

Epidemiologic Investigation

Questionnaires were completed on 92 (94%) of 98 hockey players with a single exposure (teams A, B, and C), 34 (100%) of 34 players with multiple exposures (team D), 16 (76%) of 21 cheerleaders, and 25 (96%) of 26 band members. Overall, 116 cases were identified.

Symptoms reported by at least 30% of the 69 case hockey players who had a single exposure are listed in Table 1. A typical case was characterized by acute onset of cough and dyspnea within 1 hour of playing a game at the arena. At the time of onset, the cough was frequently so severe that players had difficulty driving home after the game. The mean duration of cough was 16 days in players with acute exposure. The dyspnea was described most often as "aching lungs" or "a tightness in the chest" that made it difficult to inhale deeply. Hemoptysis was characterized by blood-tinged sputum. Similar symptoms were noted among players on team D. However, because many of the players on team D complained of chronic cough, they were not included as acute cases. The mean duration of cough for players on team D was 41 days. Eighteen (14%) of 126 hockey players reported a history of reactive airway disease (asthma). Of these, 16 (89%) reported an exacerbation of their asthma symptoms after playing at the arena.

Table 1.—Symptoms Reported by 69 Case Patients With a Single Exposure to Nitrogen Dioxide, Minnesota, 1987

Symptom	No. (%) of Patients
Cough (acute onset)	67 (97)
Shortness of breath (exertion)	45 (65)
Chest pain	44 (64)
Shortness of breath (rest)	31 (45)
Headache	31 (45)
Hemoptysis	24 (35)
Weakness	22 (32)

Attack rates for the groups are listed in Table 2. Although the attack rate for acute onset of symptoms for members of team D was only 56%, 11 (73%) of 15 players on team D who did not have acute onset of symptoms admitted to chronic respiratory symptoms (primarily cough). The attack rates for cheerleaders (who were on the ice) and band members (who sat in the stands) were similar to the attack rates for hockey players on teams A, B, and C. However, hockey players and cheerleaders were 3.2 times as likely as band members to develop hemoptysis ($P = .05$, Mantel-Haenszel χ^2 test). Length of time spent in the arena, length of time spent on the ice, and position played did not substantially increase the risk of developing hemoptysis.

Results of initial and follow-up spirometry performed on team C (single exposure), team D (multiple exposures), and the unexposed comparison group of basketball players are shown in Table 3. Overall, no differences in five lung function parameters at initial testing or at 2 months' follow-up (when comparing percent of predicted) were noted between the two hockey teams and the basketball comparison group.

Ninety-two hockey players sought medical attention; abnormal findings and treatment prescribed at the initial clinic visit are shown in Table 4. Ten patients had follow-up physician visits; none had ongoing signs or symptoms noted.

Environmental Investigation

Mechanics at the ice arena reported that the ice resurfacer had not been running properly during the preceding 6 months and that it had been emitting

Table 2 – Attack Rates Following Attendance at Hockey Games, Minnesota, 1987

Group	Total	No. (%) of Patients	
		Meeting Case Definition*	With Hemoptysis
Team A	33	27 (82)	9 (27)
Team B	29	21 (72)	6 (21)
Team C	30	21 (70)	9 (30)
Team D	34	19 (56)	4 (12)
Cheerleaders (teams A and B)	16	13 (81)	4 (25)
Band members (team A)	25	15 (62)	2 (8)
Total	**167**	**116** (69)	**34** (20)

*Defined as acute onset of cough, hemoptysis, or dyspnea.

Table 3 – Players Performing Below Normal on Initial and Follow-up Spirometry, Minnesota, 1987*

Exposure	No. (%) of Players	
	Initial	Follow-up
Single	n = 30	n = 26
FVC	0 (0)	0 (0)
FEV$_1$	1 (3)	2 (7)
FEV$_1$/FVC	5 (17)	
FEF$_{25-75}$	10 (34)	10 (34)
Peak flow	6 (21)	4 (14)
Multiple	n = 34	n = 33
FVC	3 (9)	3 (9)
FEV$_1$	2 (6)	2 (6)
FEV$_1$/FVC	4 (12)	
FEF$_{25-75}$	12 (35)	10 (29)
Peak flow	9 (26)	7 (21)
Unexposed†	n = 24	
FVC	4 (17)	
FEV$_1$	3 (13)	
FEV$_1$/FVC	0 (0)	
FEF$_{25-75}$	7 (29)	
Peak flow	4 (17)	

*FVC indicates forced vital capacity; FEV$_1$, forced expiratory volume in 1 second; and FEF$_{25-75}$, forced expiratory flow at 25% to 75% of FVC. Below normal is less than 80% predicted for FVC, FEV$_1$, FEF$_{25-75}$, and peak flow and less than 95% predicted for FEV$_1$/FVC.

†No follow-up was performed in the unexposed group.

Table 4 – Chest Auscultation and Chest Roentgenogram Findings and Treatment Prescribed for 92 Hockey Players After Nitrogen Dioxide Exposure, Minnesota, 1987

Finding and Treatment	Total No.*	No. (%) With Finding
Chest auscultation		
Rales, rhonchi, and wheezes	52	4 (8)
Chest roentgenogram		
Bilateral infiltrates	58	4 (7)
"Increased bronchial markings"	58	8 (14)
Treatment		
Antibiotics	92	22 (24)
Corticosteroids	92	19 (21)
Bronchodilators	92	7 (8)

*Chest auscultation findings noted in 52 charts and chest roentgenogram results noted in 58 charts.

elevated levels of nitrogen dioxide intermittently. Review of air quality measurements obtained between October 1986 and February 1987 indicated that a nitrogen dioxide level of 3 ppm had been recorded on November 23, 1986. At that time, exhaust fans had been turned on and subsequent measurements were within recommended limits (<0.5 ppm). All other measurements recorded in the logbook were within recommended limits. However, nitrogen dioxide levels were not measured during either of the two hockey games involved in the outbreak. During the games, the exhaust fans were not in use and, because the bleachers were not heated, the passive air vents had been blocked off to keep warm air from escaping. Responding to complaints from hockey players and spectators, arena operators turned on exhaust fans the morning after the second hockey game. When air quality measurements were obtained 2 days later, after operation of the ice resurfacer for 30 minutes, a nitrogen dioxide level of 4 ppm (eight times higher than the recommended limit) was detected.

Survey of State Health Departments

The survey of state health departments revealed that only 13 states (26%) had ever monitored indoor air quality in ice arenas. Of these, only 3 states (including Minnesota) monitor air quality on a routine basis. Although it was not possible to obtain an accurate count of the number of indoor ice skating rinks located in the United States, the Ice Skating Institute of America estimates that there are more than 800. These are located primarily in the Northeastern states, upper Midwestern states, Colorado, and California. Minnesota alone (population, 4.2 million) has 122 certified indoor ice arenas; each arena has an ice resurfacer.

COMMENT

Nitrogen dioxide exposure was the most likely cause of this outbreak of respiratory illness for the following reasons. First, the acute onset of respiratory symptoms in persons attending the two hockey games supports a toxic environmental exposure. Second, cough, hemoptysis, and dyspnea are symptoms that are typical of acute exposure to nitrogen dioxide. Finally, the ice resurfacer was found to be malfunctioning, as demonstrated by the elevated ambient levels of nitrogen dioxide detected in the ice arena after operation of the ice resurfacer 2 days later. No alteration in the machine's engine had occurred between the hockey game and the time the measurements were obtained.

Although the exact levels of nitrogen dioxide in the arena at the time of the hockey games are not known, the fact that a level of 4 ppm was detected, even after the arena ventilation system had been operating for 2 days, suggests that levels during the games may have been considerably higher. This also is supported by the following findings. High attack rates were noted for all groups interviewed. Between 21% and 30% of case hockey players experienced hemoptysis. Eighteen players reported a history of reactive airway disease (asthma), which is known to be exacerbated by nitrogen dioxide[17]; 89% of these players reported an exacerbation of their symptoms after exposure at the arena.

Although attack rates were similar for all groups, rates of hemoptysis for persons who spent time on the ice (hockey players and cheerleaders) were higher than for persons who sat in the stands (band members). The concentration of nitrogen dioxide may have been higher near the ice surface because nitrogen dioxide is heavier than air and may have settled near the ice. Also, passive airflow near the ice may have been hindered by the Plexiglas shield surrounding the ice. In addition, the hockey players and cheerleaders were exercising and therefore had a higher minute ventilation and greater lung tissue exposure than persons in the stands. While symptoms were more severe for those on the ice, the attack rate for band members, who were seated in the stands, was greater than 50%, indicating that spectators also had a clinically important exposure. No data are available on the total number of spectators at the games or the number of cases among spectators; therefore, exposure for this group was not ascertained.

Pulmonary function testing performed on members of one hockey team with a single exposure demonstrated no decrease in lung function parameters at either 10 days or 2 months after exposure. In addition, although players on the team with multiple exposures experienced more chronic respiratory symptoms than did players on the other teams, spirometry did not demonstrate a decrease in lung function in members of this team. This suggests that the level of nitrogen dioxide exposure during this outbreak, although sufficient to produce acute respiratory symptoms, was not high enough to cause long-term pulmonary damage. However, because baseline spirometry testing before exposure was not available, minor changes in pulmonary function indicative of subtle small-airway damage may have remained undetected.

Outbreaks of carbon monoxide intoxication in indoor ice arenas have occurred frequently[20,21]; however, outbreaks of nitrogen dioxide–induced respiratory illness in this setting are reported rarely. In addition to the current investigation, there are only two reports in the literature of illness compatible with nitrogen dioxide exposure in ice hockey players. In August 1969, a group of hockey players in Minnesota experienced chest tightness and difficulty breathing after playing a game.[5] In February 1988, nine persons in Quebec, Canada, experienced cough, dyspnea, and "difficulty breathing" after attending a hockey game.[22]

Despite limited documentation of similar outbreaks, it is possible that the problem of nitrogen dioxide exposure in indoor ice arenas may be more common than is recognized currently. Although 800 indoor ice arenas are located in the United States, only three states monitor the air quality on a routine basis. In addition, because respiratory symptoms associated with exposure to nitrogen dioxide may be relatively mild and nonspecific, the correct diagnosis may remain unrecognized. To prevent future outbreaks from occurring, ice resurfacing equipment must be properly maintained and ice arenas must be adequately ventilated. In addition, regulations requiring routine exhaust emission checks of ice resurfacers may be necessary. When patients present with acute onset of pulmonary symptoms, particularly hemoptysis, with onset during or shortly after spending time in an indoor ice arena, physicians should consider the possibility of exposure to nitrogen dioxide.

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Case Studies in Environmental Medicine

23 Pentachlorophenol Toxicity

Environmental ALERT . . .

☑ ***Pentachlorophenol was one of the most widely used biocides in the United States. Although it is no longer available to the general public, it continues to be an exposure risk.***

☑ ***Exposures can occur from volatilization of the chemical from treated surfaces and from skin contact with treated wood.***

☑ ***Pentachlorophenol has been found at about 235 of the more than 1,300 hazardous waste sites on the National Priorities List.***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. See page 16 for more information about continuing medical education credits and continuing education units.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
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Case Study

A 63-year-old male with weight loss, fever, dyspnea, and rash

On a hot, humid summer day, a 66-year-old male with complaints of anorexia, weight loss, flu-like symptoms, shortness of breath, and rash is brought to your office by his son. His fever, which began last evening, has been recurring since shortly after he moved to this locale to be near his son and grandchildren about 10 months ago. While the patient is at his son's home, in the company of his grandchildren, he seems to improve; yet when the patient returns to his home, he becomes ill. The son mentions that his father generally has been withdrawn and housebound since he broke his hip a year ago. The patient lives in a log cabin that has only natural ventilation and is heated by a wood stove.

Physical examination reveals a well-nourished male, sweating profusely and mildly tachypneic. He exhibits confusion and is oriented to person only. His blood pressure is 132/70 sitting, pulse 120/minute and regular, respiratory rate 24/minute and shallow without stridor. He has a rectal temperature 104.7°F. He has no cough and no vomiting or diarrhea. The skin is warm and moist; the mucous membranes are wet. There is a papular erythematous rash on the forearms bilaterally and on the neck. There is no skin discoloration, acne, or conjunctivitis. There are no focal neurologic findings, including no Kernig's or Brudzinski's signs. The lungs are clear to auscultation and percussion. There is no costovertebral tenderness. Bowel sounds are normal, and the remainder of the abdominal examination is unremarkable. You admit the patient to the hospital.

Further history reveals that the patient is a retired botanist. He had been active and generally well before the fall in which he fractured his hip. He is being treated for mild hypertension with a diuretic. There is no other significant medical or surgical history. For the past 6 months, the patient has been taking amitriptyline for depression as prescribed by his former personal physician, and he has been treating his flu-like symptoms with aspirin at the recommended over-the-counter doses. He is using calamine lotion daily on the rash. He admits to being generally withdrawn and home-bound but denies any thoughts of suicide.

Initial laboratory values show a serum pH of 7.39, Paco$_2$ 21 and Pao$_2$ 120 on 2 liters of oxygen. Serum electrolytes reveal the following: sodium 131 mEq/L (normal 135–148); potassium 5.1 mEq/L (normal 3.5–5.3); chloride 83 mEq/L (normal 95–105); and bicarbonate 21 mEq/L (normal 22–28). The anion gap is 32. Blood urea nitrogen is 32 mg/dL (normal 5–20) and creatinine 2.8 mg/dL (normal 0.7–1.5). The urinalysis is normal; urine pH is 5.5. Initial white blood count is 11.7 x 10^3/mm^3 (normal 4.5–11 x 10^3) with 61% neutrophils (normal 60%); the spun hematocrit is 47% (normal 42%–52%). Blood salicylate level of 5 mg/dL is within the therapeutic range.

Pretest

(a) What would you include in this patient's problem list?

(b) What is the differential diagnosis for this patient?

(c) Is the patient's condition due to depression? heat stroke?

(d) What further information will you seek to make a diagnosis?

Answers to the Pretest questions are on page 14.

Exposure Pathways

Pentachlorophenol (C_6Cl_5OH) and its sodium salt (sodium pentachlorophenate) are used as preservatives in the manufacture and treatment of a variety of commercial products to prevent decay from microorganisms such as fungi, mold, algae, and mosses. Treated products include particleboard, textiles, paints, adhesives, leather, latex, rubber, pulp, paper, starches, and wood. Pentachlorophenol has also been used extensively around the home as an herbicide, fungicide, weed and brush killer, disinfectant, and wood-preserving compound. Worldwide production estimates range as high as 90 million pounds; 80% of U.S. consumption is as a wood preservative, primarily for telephone and power-line poles.

☐ **In 1987, EPA banned pentachlorophenol for all nonwood products.**

A common acronym for pentachlorophenol is PCP, which is used throughout this document. The street drug phencyclidine (angel dust) is also referred to as PCP but has a different pathophysiology and has no chemical relationship to pentachlorophenol.

PCP was one of the most widely used biocides in the United States. Because of its suspected carcinogenicity, however, in 1987, the Environmental Protection Agency (EPA) banned all uses of PCP except those for wood products and restricted its availability and use to certified applicators. PCP is no longer available to the general public, which accounted for only about 3% of the amount used.

☐ **Even "untreated" lumber typically is sprayed with or dipped in pentachlorophenol before it leaves the mill.**

Most lumber produced commercially in the United States is still treated routinely with sodium pentachlorophenate solution. To control fungal growth and sap stain, a typical sawmill will apply a solution of the sodium salt to the lumber in a spray box immediately before grading and stacking. Pressure-treating wood to thoroughly impregnate it with PCP results in "penta" wood, a product commonly used to build outdoor structures such as residential fences, decks, and equipment for children's playgrounds. Penta wood is desirable because it retains its natural appearance, emanates little odor, and accepts paint easily.

Logs for use in the ground typically are treated with PCP and arsenical salts as preservatives against microorganisms and termites, then coated with creosote, a distillate of coal tar, to form a barrier to moisture and to prevent leaching of the PCP and arsenical salts. PCP has traditionally been used in log homes. Volatilization from the surface of PCP-treated products is estimated at an annual rate of roughly 2% of the total amount applied. In log homes, this volatilization rate has resulted in indoor-air contamination high enough to cause PCP-related symptoms in inhabitants.

Due to the extensive use of PCP throughout the United States, it is present in air, water, and soil. Contaminated food and water supplies are common sources of human intake, although the amounts ingested typically are small. PCP gets into water through wastewater discharges from leather tanning and textile factories, municipal wastewater treatment facilities, pulp and paper mills, and wood treatment plants. Soil contamination occurs as a result of runoff from PCP's past use as an herbicide, leaching from treated wood products and spills at industrial facilities and hazardous waste sites. PCP is a stable compound, but in water it undergoes photooxidation by sunlight (half-life 3 to 100 hours depending on pH) and can be biotransformed by microorganisms in the soil (half-life 2 to 4 weeks). One of the degradation products of PCP is tetrachlorophenol, which is also toxic.

Challenge

Additional information for the case study: For years, the patient's hobbies have included woodworking, small-boat building, and organic gardening. Because of his ill health, however, he has not done any of these activities for the past several months. He spends most of his time indoors. The patient comments that his dog is his only interest now, and the dog seems to get sick when he does.

(1) What are some clues in this case that might lead you to suspect a possible toxic environmental exposure?

Who's at Risk

The greatest risk of exposure to PCP occurs from occupational manufacture and use of the compound, especially in poorly ventilated areas. Pest-control applicators who used PCP in indoor settings were at great risk from inhalation exposures. Dermal exposure occurs primarily to those in trades or professions that handle wood, such as carpenters, electric utility-line workers, lumber-mill workers, and dock loaders. Sawmill workers are at potential risk due to inhalation of contaminated wood dust and volatilized PCP when penta wood is cut, especially freshly treated wood.

☐ **Infants and children are predisposed to increased PCP exposure by their greater surface area-to-weight ratios, as well as hand-to-mouth and play behaviors.**

☐ **Living in log homes or other structures where PCP has been used as a preservative increases risk to inhabitants.**

PCP continues to leach out of pressure-treated wood for many years. Log homes and older dwelling structures where PCP has been used as a preservative have been found to have PCP levels in indoor air exceeding those set for the workplace. Chronic exposure of occupants of log cabins and older homes has resulted in PCP toxicity.

There is some evidence that children are more susceptible to the toxic effects of PCP than adults, and that infants are even more susceptible than children, especially by the dermal route of exposure. In addition, infants and children may be at increased risk because of greater body surface area-to-body weight ratios, higher respiratory rates, hand-to-mouth behaviors, and play habits. Neonates exposed to PCP in contaminated diapers and bed linens exhibited signs and symptoms of serious poisoning.

☐ **Medications and environmental conditions that predispose a person to hyperthermia increase the risk of adverse effects to PCP-exposed persons.**

In the body, PCP acts to uncouple oxidative phosphorylation, resulting in hyperthermia. PCP-exposed workers in environments that prevent dissipation of heat from the body (e.g., high temperatures and high humidity) may be more susceptible to its acute toxic effects. Medications that cause dehydration or possess anticholinergic properties may also increase the susceptibility of exposed persons to hyperthermia. Aspirin, which can also uncouple oxidative phosphorylation when absorbed in large amounts, may enhance the risk of toxicity for PCP-exposed persons. Because PCP is highly protein-bound, persons taking medications on a long-term basis that have a high affinity for plasma proteins may be at increased risk of PCP-induced toxicity. Phenytoin, the anticoagulant warfarin, diuretics such as furosemide and ethacrynic acid, and anti-inflammatory agents such as ibuprofen and naproxen can compete with PCP for protein-binding sites, thereby increasing the level of free PCP that is circulating in the blood.

Challenge

(2) What factors could place the patient in the case study at increased risk for pentachlorophenol poisoning?

Biologic Fate

Pulmonary absorption of vapors, aerosols, and dusts are significant routes of exposure to PCP. PCP and its sodium salt are also absorbed readily via the skin and the gastrointestinal tract.

☐ **PCP is absorbed readily via the skin, respiratory tract, and gastrointestinal tract.**

Data on distribution of PCP in the body are limited; however, PCP is lipophilic, which presumably plays a role in determining its distribution. In autopsy studies, PCP was detected in the liver, kidneys, and brain, with smaller amounts in spleen and adipose tissue.

PCP is highly protein-bound in the blood and is not readily metabolized. In the liver, most PCP is conjugated to a glucuronide; a small amount undergoes oxidative dechlorination to tetrachlorohydroquinone (TCH), which has been detected in the urine of persons occupationally exposed. Ultimately, about 86% of an absorbed dose is excreted in the urine. Biliary excretion occurs in humans, but with extensive enterohepatic recirculation, only a small amount of pentachlorophenol (about 4% of an administered oral dose) is detected in the feces. Pentachlorophenol is also excreted in the milk of lactating humans and animals.

The results of studies conducted in workers suggest that the PCP excretion rate differs between acute high-level exposure and chronic low-level exposure. Elimination half-lives of about 10 hours were found in volunteers undergoing an acute (45-minute) controlled inhalation exposure, whereas the elimination half-life in chronically exposed workers on vacation was 19 to 20 days. The slower elimination of PCP in chronically exposed workers may be a result of an established equilibrium between lung, plasma protein, urine, and tissue deposits.

☐ **PCP is excreted largely unchanged in the urine; a small amount is metabolized in the liver.**

Physiologic Effects

It is believed that PCP's high degree of binding to proteins may induce conformational changes in enzymes involved in oxidative phosphorylation. Oxidative phosphorylation is the process whereby electrons generated from various sources such as the tricarboxylic acid cycle are transported down the cytochrome system. This transport normally results in the consumption of O_2 (cellular respiration) and the production of a substantial amount of energy that is captured in the production of high-energy phosphate bonds (i.e., adenosine triphosphate [ATP] bonds). The energy in these bonds is later used during other biochemical reactions.

☐ **The acute toxicity of PCP is due primarily to its ability to uncouple mitochondrial oxidative phosphorylation.**

When the formation of high-energy phosphate bonds is blocked by PCP but electron transport continues, then the process of oxidative phosphorylation is said to be uncoupled. Uncoupling results in cellular energy being released as heat, which produces hyperpyrexia. PCP also causes active transport pumps within cell membranes to fail, resulting in electrolyte gradient loss, fluid shifts, and eventual cell death.

In humans, many of the effects of acute PCP exposure are probably secondary to hyperthermia, including neurologic effects and rhabdomyolysis. In addition, metabolic acidosis can develop from accelerated aerobic metabolism.

☐ **PCP toxicity manifests primarily as a clinical syndrome of hyperthermia with associated rhabdomyolysis.**

Generally, humans are exposed to technical-grade PCP, which may be contaminated with dibenzodioxins, dibenzofurans, diphenyl ethers, chlorophenoxyphenols, and other chlorinated congeners—all of which are suspected to be carcinogenic or known to produce other adverse effects. Animal studies with both technical and purified PCP have demonstrated that many, but not all, of the toxic effects attributed to PCP are actually due to impurities.

Neurologic Effects

☐ **Neurologic effects from PCP exposure are most likely the direct result of hyperthermia.**

Human case reports of PCP exposure suggest that there are central and peripheral nervous system effects of toxicity. The neurologic effects that manifest after PCP exposure are most likely the result of hyperthermia and not a direct effect of PCP on the nervous system. Persons acutely exposed to PCP may experience lethargy, tachypnea, tachycardia, intermittent delirium, seizures, cerebral edema, focal swelling of the myelin sheath, and respiratory distress. Signs indicative of central nervous system toxicity in a 3-year-old girl exposed to PCP via the domestic water supply included intermittent delirium, fever, and convulsions. No adverse effects on the central or peripheral nervous systems have been reported after chronic occupational exposure to PCP.

Hepatic Effects

☐ **There is ample evidence of hepatotoxicity in experimental animals exposed to purified PCP.**

Hepatic toxicity in humans, as manifested by elevated serum SGOT (AST) and SGPT (ALT) levels, hepatomegaly, fatty infiltration of the liver and centrilobular congestion and degeneration, was seen after fatal and nonfatal acute exposures to PCP. However, contaminants of technical-grade PCP or exposure to other chemicals may be responsible for some of this damage. In experimental animal studies that compared the hepatic toxicity of equal doses of technical and purified PCP, the effects associated with the purified preparation were less severe than those seen with the technical grades in most cases. Some ultrastructural changes observed in the mitochondria of liver cells of the animals treated with technical-grade PCP were consistent with uncoupling of oxidative phosphorylation.

Renal Effects

In humans and animals, PCP exerts a minor toxic effect on the kidneys, producing only mild and transient disturbances. Workers at a wood-treatment facility had reduced glomerular filtration rates and mild tubular degeneration, which were reversible when exposure ceased. Other evidence of renal dysfunction in humans, such as impaired acid-base balance, may be secondary to hyperthermia. In animals, little or no consistent difference was seen between technical-grade and purified PCP with regard to severity of renal effects.

☐ **Renal effects from PCP exposure are mild and transient.**

Carcinogenicity

There is no convincing evidence from epidemiologic studies that PCP causes cancer in humans. Case reports suggest a possible association between cancer (Hodgkin's disease, soft-tissue sarcoma, and acute leukemia) and occupational exposure to technical-grade PCP. However, in all of these cases, concurrent exposure to other toxic substances may have contributed to the effects. In a study by the National Toxicology Program (NTP), pure PCP showed oncogenic activity in mice. The International Agency for Research on Cancer (IARC) considers the evidence for carcinogenicity of PCP in humans limited, and the evidence for carcinogenicity in animals inadequate. The EPA carcinogenic classification for PCP is "probable human carcinogen," but this classification is currently under review.

☐ **Case reports suggest that an association exists between technical-grade PCP and Hodgkin's disease and soft-tissue sarcoma.**

Other Effects

Chronic exposure to technical-grade PCP has been associated with chloracne—an acneiform rash around the eyes, temples, and forehead. This skin condition, as well as many other effects of PCP, has been attributed to various contaminants in technical-grade PCP, particularly dioxins and dibenzofurans. Pemphigus vulgaris and urticaria (skin diseases with an immunologic pathophysiology) have been reported in several cases of nonoccupational exposures. Depigmentation (or vitiligo) and irritant dermatitis have been associated with chronic exposure to PCP-containing germicides. Low-level chronic exposures to airborne PCP can cause irritation of the eyes, nose, throat, and lungs.

☐ **Other reported effects of PCP exposure include skin lesions and hematologic abnormalities. Most of these effects may be due to the impurities in technical-grade PCP.**

Case reports have been published of hemolytic anemia and aplastic anemia with subsequent acute leukemia or Hodgkin's disease. The exposures were predominantly dermal exposures to technical-grade PCP. The mechanism for these hematologic effects appears to be a direct action on blood-forming tissue. The reported anemia is unlikely to be caused by uncoupling of oxidative phosphorylation because no signs of hyperthermia were observed in these cases.

Animals exposed to technical-grade PCP exhibited hematologic effects that generally were not observed when the animals were administered pure PCP.

There is no evidence that PCP exposure results in human embryotoxicity or teratogenicity. In experimental animals, PCP is not teratogenic but is embryotoxic and fetotoxic at exposure levels that cause maternal toxicity.

Challenge

Additional information for the case study: Suspecting an environmental toxic exposure, you contact an environmental toxicologist at the state health department. After discussing the patient and his symptoms, the specialist suggests poisoning caused by an organophosphate pesticide, dinitrophenol, or pentachlorophenol.

(3) What is the reasoning that leads you to narrow the diagnosis to pentachlorophenol poisoning?

Clinical Evaluation

History and Physical Examination

☐ **A thorough environmental and occupational history may reveal a possible PCP exposure in cases in which hyperthermia occurs.**

The history of a person who has possible PCP exposure should include information about other precipitating factors for hyperthermia such as age; clothing; environmental temperature and humidity; medications with anticholinergic effects, such as phenothiazines, antihistamines, and antidepressants; medications that predispose to dehydration, such as diuretics; medications or chemicals that uncouple oxidative phosphorylation, such as salicylates or dinitrophenols; and medications that interfere competitively with protein binding, such as warfarin, phenytoin, furosemide, and ibuprofen. A thorough environmental and occupational history should be obtained, including information about hobbies or projects such as woodworking and gardening. (See *Case Studies in Environmental Medicine: Taking an Exposure History*.)

Because PCP-intoxicated patients may not give the appearance of having an elevated temperature, the physical examination must include a core body temperature. In addition, blood pressure and heart and respiratory rate should be determined. The liver, kidney, and central nervous system may be affected by PCP exposure. Because exposure to technical-grade PCP has been associated with chloracne and other skin conditions, respiratory irritation, and blood dyscrasias, the skin, respiratory tract, and blood should be evaluated.

Signs and Symptoms

Acute Exposure

Acute exposure to PCP is associated with hyperthermia, which produces a generalized spectrum of toxicity, including anorexia, fatigue, thirst, fever, profuse diaphoresis, tachypnea, tachycardia, nausea, vomiting, and abdominal pain. In severe poisonings, severe muscle spasms and rigidity, as well as seizures, may occur. Hepatic enlargement has been reported in adults and infants exposed to PCP-containing compounds. Hepatic toxicity has been further manifested in adults by increased SGOT (AST) and SGPT (ALT), fatty degeneration, and congestion. Intravascular hemolysis and aplastic anemia have been associated with PCP exposure in case reports. There is no significant staining of the skin after dermal contact with PCP as there is with dinitrophenols, which also cause uncoupling of oxidative phosphorylation.

☐ **Most signs and symptoms of acute PCP poisoning are the result of hyperthermia.**

Chronic Exposure

In addition to nonspecific signs and symptoms, such as fever and malaise, chronic occupational exposure to high levels of PCP vapor, as well as to aerosols, has been associated with conjunctivitis, chronic sinusitis, bronchitis, and reduced glomerular filtration and tubular function. There is evidence of elevated SGOT and SGPT levels in workers after chronic, predominantly dermal, exposure to PCP. Most of these conditions are reversible after exposure ceases. One group of workers with chronic PCP exposure had a high incidence of chloracne, most likely due to PCP contaminants.

☐ **Nonspecific signs and symptoms such as fever, anorexia, weight loss, and fatigue characterize chronic PCP exposure.**

Laboratory Tests

Direct Biologic Indicators

In one study, the general population had average levels of 4 micrograms of PCP per deciliter (μg/dL) of blood and 5 micrograms of PCP per liter (μg/L) of urine. In studies of workers using PCP or PCP-treated materials (e.g., workers involved in construction of log homes, repair of telephone lines, custodial care of log cabin museums, application of pesticides) PCP blood levels ranged from 8.3 to 5,760 μg/dL and urinary levels ranged from 120 to 10,000 μg/L.

☐ **PCP can be measured in urine and blood.**

Residents of log homes treated with PCP preservatives had mean levels of 42 µg/dL in blood and 69 µg/L in urine; PCP blood levels of children who resided in log homes were 1.8 times the blood levels of their parents.

When monitoring urine levels, relating the PCP concentration to the amount of creatinine in the sample (i.e., µg PCP per gram of creatinine [µg/g creatinine]) corrects for variations in urine concentration. The American Conference of Governmental Industrial Hygienists (ACGIH) suggests that the biological exposure index (BEI) guideline for PCP in the workplace be 1,000 µg/g creatinine.

Indirect Biologic Indicators

In PCP poisoning, laboratory evaluation should include tests for hepatic and renal dysfunction, electrolyte imbalance, hemolytic anemia, and metabolic acidosis. Testing of immune function is not warranted in the clinical management of PCP exposure.

Challenge

Additional information for the case study: You tell the patient and his son that the patient's symptoms are consistent with pentachlorophenol exposure and the source may be the logs of the cabin.

(4) What tests can help you confirm your suspicion?

(5) What further laboratory evaluation is appropriate for the patient, assuming his condition is due to pentachlorophenol exposure?

(6) The son asks you if his father's exposure to pentachlorophenol is increased by using throat lozenges; the label says the lozenges contain 50 milligrams of phenol per lozenge. What will you tell him?

Treatment and Management

Acute Exposure

The treatment of pentachlorophenol poisoning is supportive. The onset of toxicity may be sudden in persons with significant exposure. Thus, it will be necessary to stabilize the patient with maintenance of the airway, breathing, and circulation. Patients who have seizures will require pharmacotherapy with benzodiazepines. If intubation is necessary, general anesthesia or paralysis may be required to reduce injury or prevent death during the procedure. Gastric lavage will be useful only if the patient has recently ingested the substance. Activated charcoal has been shown to bind most phenolic compounds; repeated dosing may be useful in preventing absorption and in interrupting enterohepatic recirculation. Cholestyramine resin was also used for this purpose in primates, but its effectiveness in humans is unknown. Forced diuresis has been proposed as enhancing the elimination of PCP; however, the clinical evidence to justify this therapy is lacking and volume depletion in patients with hyperthermia should be avoided.

After removal from exposure and decontamination, cooling the patient is of the utmost importance in the treatment of hyperthermia. The patient's temperature can be reduced with an ice-water bath or repeated washes with cool water in front of fans.

Chronic Exposure

Treatment of chronic pentachlorophenol poisoning involves removal from the source of exposure.

Challenge

(7) What treatment would you recommend for the patient in the case study? What follow-up measures would you recommend for managing this case?

ATSDR

Standards and Regulations

Workplace

The Occupational Safety and Health Administration (OSHA) has set a permissible exposure limit (PEL) for PCP of 0.5 milligrams per cubic meter (mg/m^3) of air as an 8-hour time-weighted average (TWA). OSHA also gives PCP a "skin" designation, which indicates the potential for dermal absorption. The National Institute for Occupational Safety and Health (NIOSH) has determined the level immediately dangerous to life and health (IDLH) to be 150 mg/m^3 in air.

Environment

In 1984, EPA restricted the use of PCP to wood products. In addition, EPA set restrictions on the dioxin levels allowed in pentachlorophenol products.

The EPA maximum contaminant level (MCL) for PCP in drinking water is 1 μg/L (1 part per billion [ppb]); the EPA maximum contaminant level goal (MCLG) is 0 μg/L. Several states have guidelines for drinking water ranging from 6 to 220 μg/L. The World Health Organization (WHO) guideline for PCP in drinking water is 10 μg/L (10 ppb).

The Food and Drug Administration (FDA) lists PCP as safe for use as a component of adhesives intended for use in packaging, transporting, or holding food.

Suggested Reading List

Clinical

Wood S, Rom WN, White GL, Logan DC. Pentachlorophenol poisoning. J Occup Med 1983;25(7):527-30.

Exon JH. A review of chlorinated phenols. Vet Hum Toxicol 1984;26(6):508-20.

O'Malley MA, Carpenter AV, Sweeney MH, et al. Chloracne associated with employment in the production of pentachlorophenol. Am J Ind Med 1990;17:411-21.

Epidemiology

Gilbert FI, Minn CE, Duncan RC, Wilkinson J. Effects of pentachlorophenol and other chemical preservatives on the health of wood treating workers in Hawaii. Arch Environ Contam Toxicol 1990;19:603-9.

Enarson DA, Chan-Yeung M, Embree V, et al. Occupational exposure to chlorophenates. Scand J Work Environ Health 1986;12:144-8.

Thind KS, Karmali S, House RA. Occupational exposure of electrical utility linemen to pentachlorophenol. Am Ind Hyg Assoc J 1991;52(12):547-52.

Cline RE, Hill RH Jr, Phillips DL, et al. Pentachlorophenol measurements in body fluids of people in log homes and workplaces. Arch Environ Contam Toxicol 1989;18:475-81.

Toxicology

Williams PL. Pentachlorophenol, an assessment of the occupational hazard. Am Ind Hyg Assoc J 1982;43(11):799-810.

Seiler JP. Pentachlorophenol. Mutat Res 1991;257:27-47.

Related Government Documents

Agency for Toxic Substances and Disease Registry. Toxicological profile for pentachlorophenol [update]. Atlanta: US Department of Health and Human Services, Public Health Service, 1993.

Environmental Protection Agency. Drinking water criteria document for pentachlorophenol. Washington, DC: US Environmental Protection Agency, Office of Drinking Water, 1989. Report no. EPA 600/x 84-177-1.

Sources of Information

More information on the adverse effects of pentachlorophenol and treating cases of exposure can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Pentachlorophenol Toxicity* is one of a series. To obtain other publications in this series, please use the order form on the inside back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of the Director, at (404) 639-6204.

Answers to Pretest and Challenge Questions

Pretest
Pretest questions begin on page 1.

(a) The patient's problem list is as follows:

- Fever of undetermined cause (hyperthermia)
- Mildly altered mental status
- History of depression, currently under treatment
- History of hypertension, currently under treatment
- Electrolyte abnormalities
- Azotemia
- Erythematous rash

(b) The differential diagnosis for a patient who has high fever, tachypnea, and mildly altered mental status must include acute overwhelming infections such as pneumonia, meningitis, or urinary tract infection. In addition, the patient might be suffering from heat stroke and heat exhaustion (see [c] below), or he may be suffering from hyperthermia due to medications or chemical exposure. Heat-related disorders are exacerbated by dehydration and diuretic use.

(c) No; depression would not cause fever, electrolyte abnormalities, azotemia, or rash. However, the medications he is taking for depression may be contributing factors. Heat stroke is unlikely because this condition is usually characterized by relatively dry skin and dry mucous membranes, and this patient is suffering from diaphoresis.

(d) Before making a diagnosis, you should explore the conditions in the differential diagnosis. Infection should be ruled out early in the management of this case; you may need to perform a lumbar puncture and obtain blood and urine cultures. A chest X ray, urinalysis, intravenous pyelogram, and liver function tests may provide information to help exclude conditions in the differential diagnosis. Resources to explore chemical poisonings can be found at your local or state health department, ATSDR, and the regional poison control center.

Challenge
Challenge questions begin on page 3.

(1) Some clues that indicate a possible environmental exposure, particularly in the home, include the following: (1) a temporal relationship between the patient's onset of symptoms and presence in the home, and (2) the simultaneous illness of the patient and his dog. It is not uncommon for illnesses in pets to suggest toxic environmental exposures. (See *Case Studies in Environmental Medicine: Taking an Exposure History.*)

(2) Any factors that contribute to hyperthermia could increase the risk for PCP poisoning. Factors for the patient in the case study include the following: the age of the patient; environmental conditions (the heat and humidity) that prevent heat dissipation; the use of a diuretic (which could enhance dehydration and increase the amount of circulating PCP by competing with it for protein-binding sites); the use of a tricyclic antidepressant (which has anticholinergic effects); and the use of aspirin (which causes further uncoupling of oxidative phosphorylation if taken in excessive amounts).

(3) Organophosphate pesticides, whose mechanism of action is based on acetylcholinesterase inhibition, may cause a syndrome of cholinergic excess consisting of salivation, lacrimation, urination, and defecation (SLUD). A full cholinergic syndrome is not seen in this patient. In addition, excessive gastrointestinal symptoms and bronchospasm are not present. Patients who have organophosphate pesticide poisoning typically are

tachypneic from excess pulmonary secretions and bronchospasm; a high temperature is atypical. If necessary, a red blood cell (RBC) count and a plasma cholinesterase level can be obtained. However, even if the cholinesterase results are within normal range, tests should be repeated in a few days to determine the change in values. (See *Case Studies in Environmental Medicine: Cholinesterase-Inhibiting Pesticide Toxicity.*)

Dinitrophenol is present in the insecticide Dinoseb.* Like pentachlorophenol, the pathophysiology of dinitrophenol also involves the uncoupling of oxidative phosphorylation; therefore, poisoning due to these two chemicals would cause similar symptoms. A thorough and careful history would be necessary to exclude the possibility of current contact with the insecticide. Being a botanist by profession and a gardener by hobby, the patient should have an awareness of insecticides he has used, especially those used over a long period of time. Another feature that distinguishes the two chemicals is the staining property. Yellow stains appear on the skin after dermal contact with dinitrophenol; no staining occurs with pentachlorophenol.

(4) To confirm your suspicion of a PCP exposure, you could recommend that the patient's home be tested for airborne levels of PCP. Walls in a room treated with PCP release the chemical into the air, with concentrations reaching 1 nanogram per cubic meter (ng/m^3) of air on the first day after treatment and 160 ng/m^3 on the fourth day. PCP is no longer used in the treatment of wood products intended for use in the interior of residences, but many log cabins and older homes were built before enforcement of regulations that restricted PCP use.

Biologic tests on the patient could also confirm your suspicion. If the exposure is ongoing, urine and blood levels of PCP would be elevated (see *Laboratory Tests*, page 10).

(5) If the patient has PCP poisoning, further laboratory tests could be performed to evaluate the hepatic, renal, and hematologic systems.

(6) Phenol could easily be confused with PCP, especially because they have both been used as disinfectants and preservatives. Phenol is found in many over-the-counter and prescription medications (e.g., ointments, ear and nose drops, cold-sore lotions, mouthwashes, lozenges, gargles, toothache medications, and analgesic rubs) at concentrations of 0.5% to 1.5%. However, the action of phenol and PCP in the body is quite different. PCP primarily acts to uncouple oxidative phosphorylation with resultant hyperthermia. Phenol is primarily a caustic, causing protein denaturation and coagulation.

(7) After initiating acute care (i.e., establishing an intravenous line, administering antibiotics, and instituting cooling treatments), the priority in treating this patient is to prevent further exposure to PCP. This can be accomplished by relocating the patient or by decreasing the level of PCP inside the log cabin. Ensuring adequate ventilation indoors would help, and application of a barrier wood finish such as clear polyurethane to the indoor surfaces of the log cabin would decrease volatilization of the PCP.

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* Use of trade names is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services or the Public Health Service.

CLINICAL OBSERVATION

Aldicarb Poisoning

A Case Report With Prolonged Cholinesterase Inhibition and Improvement After Pralidoxime Therapy

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Aldicarb is the most potent of the commercially available carbamate pesticides and is an unusual source of acute human poisonings. We present the case of a 43-year-old man exposed to aldicarb who developed severe cholinergic symptoms and progressive weakness requiring intubation for 5 days. Both his red blood cell cholinesterase and plasma pseudocholinesterase levels were depressed for a minimum of 44 hours. He demonstrated neuromuscular improvement concurrent with pralidoxime administration. The pertinent medical literature on aldicarb poisoning is reviewed. *(Arch Intern Med. 1994;154:221-224)*

Both carbamate and organophosphate pesticides cause a decrease in cholinesterase activity, which can be measured through red blood cell (RBC) cholinesterase and plasma pseudocholinesterase levels. Carbamate pesticide poisonings tend to be less severe because they bind reversibly to the active site on the cholinesterase enzyme, in contrast to the organophosphate pesticides that, over time, bind irreversibly. Carbamate poisoning causes the same excess in muscarinic stimulation and nicotinic stimulation followed by weakness seen in organophosphate poisonings, but for a relatively shorter duration. Pralidoxime is generally not used for treating carbamate poisonings, and in some animal studies has reportedly worsened the clinical course.[1,2]

Aldicarb (2-methyl-2-[methylthio] propionaldehyde-O-[methylcarbamoyl]-oxime) was first distributed in the United States in 1970 by the Union Carbide Corp (Danbury, Conn) under the trade name Temik. It is now produced by Rhône-Poulenc Ag Co (Research Triangle Park, NC) in both dust-free gypsum granules and low-dust corn cob grit formulations. Its primary use is as a treatment incorporated into the soil against nematodes, mites, and insects. It is taken up systemically by plants. A 1988 estimate of the amount of aldicarb applied annually in the United States was 5.2 to 5.7 million pounds.[3] It is registered for use on cotton, sugar beets, sugar cane, potatoes, sweet potatoes, peanuts, oranges, pecans, dry beans, soy beans, and ornamental plants.[4]

Aldicarb has an LD$_{50}$ (median toxic dose) of 0.8 mg/kg in rats,[5] which makes it the most toxic on a per weight basis of any of the commercially available carbamate pesticides. Severe clinical poisonings with aldicarb are uncommon and therefore clinical experience in treatment is limited. This case describes a severe aldicarb poisoning with prolonged RBC cholinesterase and plasma pseudocholinesterase inhibition, and improvement temporally associated with pralidoxime administration.

REPORT OF A CASE

A 43-year-old previously healthy man suddenly developed severe nausea, vomiting, and diarrhea 15 to 20 minutes after eating dinner. He was profoundly weak, had slurred speech, and complained of continually needing to clear his throat be-

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cause of abundant secretions. His wife and child were not affected. He denied previous medical problems or taking medications. However, over the previous 6 months he had had several similar episodes, one of which required emergency treatment and resolved spontaneously over several hours.

The paramedics responded and found the patient combative, cyanotic, incontinent of stool and urine, vomiting, salivating, and lacrimating excessively. He was bradycardic with a pulse rate of 50 beats per minute and a stable blood pressure. He was washed down, given 5 mg of atropine intravenously, and transported to a local hospital. On arrival his blood pressure was 155/122 mm Hg, with a pulse rate of 127 beats per minute, a respiratory rate of 20, and a temperature reading of 36.9°C. He was alert but mildly confused.

The patient's clothes were removed and he was showered to remove any possible skin contamination. Gastric lavage was performed and 1 g/kg of body weight of activated charcoal with sorbitol was administered. Results of his initial laboratory studies were remarkable for a serum potassium concentration of 2.6 mmol/L, a serum carbon dioxide concentration of 19 mmol/L, and an anion gap of 19. Over a 2-hour period he received potassium supplements, 4 mg of atropine, and 1 g of pralidoxime intravenously prior to being transported to a tertiary facility.

ON ARRIVAL at the tertiary hospital his vital signs had normalized with a blood pressure of 130/100 mm Hg, a pulse rate of 90 beats per minute, a respiratory rate of 20, and a temperature of 34.8°C. He was alert but disoriented to time. His skin was diaphoretic and pale. He had pinpoint pupils, twitching of the eyelids, fasciculations of the facial muscles and tongue, bibasilar rales, and hypoactive bowel sounds. His neurologic examination revealed profound weakness and clonus that was greatest on the right side. He was able to lift his left arm against gravity but was limited to moving his fingers on the right side. Sensation and deep tendon reflexes were intact. Thiocyanate, tylenol, aspirin, iron, and lactate levels were within normal limits. Results of noncontrasted computed tomographic scan of the head and lumbar puncture were unremarkable.

After admission he became progressively weaker and had difficulty clearing his secretions. Arterial blood gases drawn 7 hours after admission demonstrated a pH of 7.32, a P_{CO_2} of 32.9 mm Hg, and a P_{O_2} of 72.1 mm Hg on 4 L/min of oxygen administered by nasal cannula. Owing to progressive worsening of the patient's clinical status, he received a second treatment of 1 g of pralidoxime intravenously. Twenty minutes after the bolus of pralidoxime, and 10 hours after onset of his symptoms, he had a 3-minute tonic-clonic seizure that resolved spontaneously and was treated with 5 mg of diazepam intravenously. His condition continued to worsen, and 30 minutes later he was intubated after pretreatment with 80 mg of succinylcholine intravenously and thiopental intravenously for failure to maintain his airway. He was given two additional treatments of 1 g of pralidoxime intravenously over a 30- to 60-minute period within a 6-hour period followed by an infusion of 0.5 g per hour over a 40-hour time frame. His strength began to improve after the drip was initiated, more than 16 hours after the onset of his symptoms. He progressed from only moving his fingertips to moving his entire right arm and writing notes within 60 minutes of starting the infusion. The initial pralidoxime infusions were temporally associated with hypertensive episodes to as high as 195/100 mm Hg. The continuous infusion did not elevate his blood pressure.

Cholinesterase Concentrations*

Time (Hours†)	Plasma	Red Blood Cell
02.00 (6)	469	
16.30 (44)	3107	6.4
06.00 (58)	7287	
04.00 (80)	7144	
06.00 (130)		13.7
20.00 (168)	8719	11.5
22 days	8320	11.8

**Normal range: plasma (4499 to 13 320 U/L); red blood cell (9.9 to 18.0 IU/mL).*
†Hours after the onset of symptoms.

Concurrent with the pralidoxime administration, the patient was given an additional 2 mg of atropine intravenously, followed by an atropine drip of 0.5 mg/h for 22 hours. During this time he became severely agitated and required sedation. The atropine was stopped. Fifteen hours later he was given 0.25 mg of glycopyrrolate mg per hour for 9 hours to control continued excess secretions while limiting central nervous system effects. He developed a temperature of 39°C, presumably from aspiration pneumonia, and was given 2 million units of penicillin per hour intravenously, 1 g of cefotaxime every 8 hours, and 1 g of vancomycin every 12 hours.

The RBC and plasma cholinesterase levels are presented in the **Table**. His initial plasma cholinesterase level 6 hours after onset of symptoms was 469 U/L (6% of normal) and did not increase to the normal range for another 52 hours. The initial RBC cholinesterase level 44 hours after admission was 6.4 U/mL (54% of normal). A repeated level 4 days later was 13.7 U/mL, and follow-up tests remained normal.

His condition gradually improved and he was extubated on the fifth day of hospitalization. After extubation, discussions with the patient and his family raised the possibility of poisoning with aldicarb (Temik). The earliest available blood sample, collected 15 hours after onset of symptoms, had an aldicarb concentration of 0.1 μg/mL, an aldicarb sulfoxide concentration of 1.7 μg/mL, and an aldicarb sulfone concentration of 3.4 μg/mL. A urine screen for 22 common organophosphate pesticides (National Medical Services Inc, Willow Grove, Pa) collected on the day of admission failed to demonstrate any concurrent exposure. The patient had an uneventful recovery, and on follow-up visits has remained asymptomatic.

COMMENT

Aldicarb is the most potent of the commercially available carbamate pesticides. It is absorbed through the skin, lungs, and gastrointestinal tract. In human trials, doses of 0.1 mg/kg produced symptoms,[6] and doses of 0.025 mg/kg demonstrated the lowest observed effect level for cholinesterase inhibition.[7] In the California watermelon-borne aldicarb poisonings, symptoms were reported at doses as low as 0.021 mg of aldicarb per kilogram of body weight.[8]

Aldicarb is rapidly absorbed via the gastrointestinal tract. After large doses the onset of symptoms may occur as quickly as 5 minutes.[9] It is rapidly metabolized to aldicarb sulfoxide and then more slowly to aldicarb sulfone, as well as a number of additional metabolites. Both aldicarb sulfoxide and aldicarb sulfone are pharmacologically active, with the potency of aldicarb sulfoxide roughly equivalent to its parent compound. The potency of aldicarb sulfone is much less that of aldicarb.[10] As with most carbamates, aldicarb has a short half life, and in 24 hours 80% to 90% of an ingested dose in the rat is excreted in the urine.[11]

Because of its method of application as a treatment injected into the soil, aldicarb is unlikely to cause inadvertent acute toxic effects to bystanders. It is systemically absorbed by plants, and therefore consumption of certain improperly treated crops may result in exposure. Soil application has also resulted in a number of reports of ground water contamination.[12-14] Individuals working directly with the production and application of aldicarb may become inadvertently poisoned.

The source of the aldicarb poisoning in our patient is not entirely clear. His history was not suggestive of any occupational source of exposure. Because of the sudden onset and severity of his gastrointestinal symptoms, and his lack of any known source of significant respiratory or dermal exposure, it is most reasonable to assume that he ingested the poison. The onset of his symptoms 15 to 20 minutes after eating suggests that his dinner was contaminated. The patient and the police were informed of our concerns.

Only a small number of life-threatening human aldicarb poisonings have been reported. In the first reported case of accidental poisoning, the wife of a corporate scientist developed cholinergic symptoms, muscle fasciculations, and difficulty breathing after ingesting a mint sprig growing near an aldicarb-treated rose bush.[15] A 36-year-old woman who ingested one teaspoon of aldicarb in a suicide attempt developed marked cholinergic signs and symptoms with neuromuscular weakness. However, details of her treatment and hospital course were not given.[16] A 7-month-old infant developed convulsions and cyanosis after exposure to aldicarb powder. She was intubated overnight and required treatment with more than 100 mg of atropine.[17]

Aldicarb is the most potent of the commercially available carbamate pesticides.

Reported deaths from aldicarb poisoning are extremely rare. A farm worker in California was crushed by a tractor while lying in a field after working with aldicarb without proper protection. Postmortem blood samples contained 0.108 parts per million of aldicarb sulfoxide and 0.374 parts per million of aldicarb sulfone, with a total concentration roughly one tenth of that in our patient. The total body burden was calculated to be 0.275 mg/kg.[18] The cause of death was listed as trauma but the aldicarb exposure may have incapacitated him. At least three other deaths have been documented.[18]

Other aldicarb exposures have been associated with the ingestion of contaminated commercial food products. Aldicarb-contaminated watermelon produced clinical illness in California, Oregon, and Washington.[19] In California there were 690 probable poisonings and 370 possible poisonings. Clinical findings included seizures, loss of consciousness, dysrhythmias, hypotension, dehydration, and anaphylaxis.[20] Cases of illness from the consumption of aldicarb-contaminated cucumbers have also been reported,[19,21] and contaminated potatoes have been reported.[22] In a bizarre occurrence, 23 cows were killed by consuming feed that had been intentionally poisoned with aldicarb.[23]

Carbamates exert their toxic effect by inhibiting cholinesterase enzymes, with the resultant cholinergic excess and muscular weakness due to the effects of increased acetylcholine on nerve conduction. Unlike organophosphate chemicals, which may bind irreversibly, the carbamate chemicals bind reversibly, and therefore tend to have a shorter duration of action. Aldicarb exposure in humans inhibits both RBC cholinesterase and plasma pseudocholinesterase. Ingestion of 0.1 mg/kg resulted in a reduction of whole-blood cholinesterase activity to 28% of baseline within 2 hours of ingestion, with resolution of symptoms by 4 hours.[6] In vitro the half life of cholinesterase inhibition activity is 30 to 40 minutes.[24] In rats, drinking water concentrations of 19.2 parts per million of a 1:1 mixture of aldicarb sulfoxide and aldicarb sulfone resulted in a decrease in plasma pseudocholinesterase levels to 23% to 32% of normal with a decrease in RBC cholinesterase to 37% to 43% of normal.[25]

The treatment of carbamate poisonings is supportive in the majority of cases. Patients with dermal exposures should have their contaminated clothing removed and the involved skin cleansed with alkaline soap and water, with appropriate care to prevent exposure of the medical staff. For ingestions, gastric lavage and the administration of activated charcoal are recommended. In severe poisonings atropine may be useful in controlling secretions, and large quantities may be required. Since carbamates do not readily cross the blood-brain barrier, glycopyrrolate may be substituted for atropine to avoid significant central neurologic effects. Administration of cholinergic drugs, such as the succinylcholine given in our patient, should be avoided in carbamate poisonings.

The use of pralidoxime for carbamate pesticide poisoning is controversial. Most carbamate poisonings resolve within several hours without treatment other than atropine. Since the binding to cholinesterase enzymes is reversible, there is usually no need for oxime therapy. Clinical worsening after administration of pralidoxime, toxogonin, and obidoxime to animals has been described in animal experiments with the carbamate pesticide carbaryl.[1,2] Obidoxime also interfered with the protective effect of atropine in carbaryl poisonings.[2] However, for aldicarb poisoning, pralidoxime and obidoxime have been shown to improve mortality in rats,[2] and toxogonin reduced toxicity in rats.[1] In our patient we noted hypertension with the bolus administration of pralidoxime, but not with continuous intravenous infusion. While it is impossible to determine if the patient's seizure was related to the second dose of pralidoxime, his clinical status was clearly deteriorating prior to the pralidoxime with documented acidemia and progressive difficulty maintaining his airway. Subsequent doses of pralidoxime appeared to improve our patient's weakness without significant adverse effects.

In summary, we presented an unusual case of severe poisoning with aldicarb, a carbamate pesticide. To our knowledge, this is the first article on prolonged cholinesterase inhibition with aldicarb poisoning, and documents the highest combined blood concentration of aldicarb and its metabolites of any human poisoning in the medical literature. The patient appeared to benefit from oxime therapy, demonstrating neuromuscular improvement temporally associated with pralidoxime administration. Severe aldicarb poisonings may be life threatening and can be successfully managed in the same manner as organophosphate poisonings.

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Case Studies in Environmental Medicine

22

Cholinesterase-Inhibiting Pesticide Toxicity

Environmental ALERT . . .

- ☑ ***The molecular targets of organophosphate and carbamate pesticides are cholinesterases, particularly acetylcholinesterase, an enzyme that controls the transmission of nerve impulses at synapses.***
- ☑ ***In the United States in 1989, organophosphate toxicity accounted for 38% of all treated pesticide-related cases and at least seven fatalities.***
- ☑ ***Cholinesterase-inhibiting pesticides can cause fatalities by dermal contact, as well as by inhalation and ingestion.***
- ☑ ***Poisonings of children can be greatly reduced by proper labeling and storage of pesticides.***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. See page 23 for more information about continuing medical education credits and continuing education units.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

A 30-year-old, comatose male with miosis, diaphoresis, and incontinence

You are alerted that a 30-year-old, unconscious male is being brought by ambulance to the Emergency Department where you are on duty. While at home, the patient suddenly developed headache, dizziness, weakness, nausea, vomiting, and diarrhea. En route to the Emergency Department, he lost consciousness and experienced urinary and fecal incontinence.

When the patient arrives at the Emergency Department, you note that he has fixed pinpoint pupils, generalized paralysis, fasciculations, and is unresponsive to deep pain. Corneal and gag reflexes are absent. He has profuse salivation, diaphoresis, and excess lacrimation. Vital signs include the following: blood pressure 140/90 mm Hg, temperature 99.2°F (37.2°C), pulse 58 beats/minute and regular. Rales are noted during chest auscultation. Heart examination is unremarkable except for an S_4 gallop. Abdominal examination reveals no detectable masses, organomegaly, or hyperactive bowel sounds. Mucoid secretions are suctioned from the trachea at the time of intubation, and mechanical respiratory support is instituted. You initiate treatment with Narcan* for possible opiate ingestion, with no effect.

From the patient's brother, you learn that the patient returned yesterday from a 5-day vacation in Arizona. This morning he changed into work clothes and began mixing pesticides for subsequent tree spraying in their family orchard. About noon, the patient became nauseated and started sweating profusely. The brother cannot recall any unusual events before his brother's illness and assures you that they had performed the tree-spraying operations many times in the past with no ill effects.

After treatment and antidotal therapy, the patient improves remarkably–he has spontaneous respirations and regains consciousness within 4 hours. Mechanical ventilation is discontinued, and the patient is well enough to be discharged 3 days after admission.

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* Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

Pretest

(a) *What should be included in this patient's problem list? What is the differential diagnosis?*

(b) *What important information did the patient's brother provide? What further information will you seek?*

(c) *What laboratory tests could you order to confirm your diagnosis?*

(d) *What was the treatment and antidotal therapy that resulted in the patient's remarkable recovery?*

Answers to the Pretest questions are on page 21.

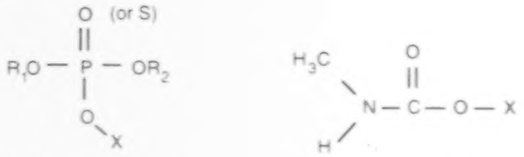
Exposure Pathways

- **Most occupational pesticide poisonings result from dermal contact during handling or contact with residues on sprayed plants and soils.**

- **As insects develop greater resistance to insecticides, new toxic compounds are necessary.**

The use of organophosphate and carbamate compounds (Figure 1) as insecticides began in the 1930s and has increased markedly since many organochlorine insecticides were banned in the 1970s. In contrast to organochlorine insecticides, organophosphate and carbamate insecticides degrade rapidly in the environment and do not accumulate or concentrate in the food chain. Thus, organophosphate and carbamate insecticides have less potential for chronic health effects or environmental contamination than do organochlorine insecticides and pose less risk to consumers of food products. However, organophosphate and carbamate compounds have a greater potential for acute toxicity in humans than do chlorinated compounds. Even among the organophosphate or carbamate pesticides, however, a wide spectrum of potency exists. As insects develop greater resistance, the trend is to use more potent, and consequently, more lipid-soluble and longer-lasting insecticides.

Figure 1. General chemical structures of organophosphate and carbamate pesticides



A. Organophosphate*

B. Carbamate

* R_1 and R_2 are usually alkyl groups (typically ethyl or methyl). X is also commonly an alkyl group that is replaced by a hydrogen atom during the "aging" of the organophosphate-enzyme complex. Pesticides that have a sulfur in place of the oxygen double-bonded to the phosphorus are called thiophosphates.

- **Improper storage of pesticides often leads to accidental ingestion and contact by children and adults.**

Most organophosphate and carbamate insecticides are used for crop spraying in commercial agriculture. Approximately 75% of all insecticides are used on three crops: cotton, corn, and soybeans. Ethyl parathion (Parathion), which will soon be phased out of production, and malathion are the most widely used organophosphate insecticides. Aldicarb (Temik) and carbaryl (Sevin) are well-known carbamate insecticides. Organophosphate and carbamate compounds degrade in the environment at varying rates; half-lives range from days to months, although generally they are longer in dry climates and at low temperatures.

Most occupational exposures to organophosphates and carbamates occur from skin absorption, although inhalation may be an important route of exposure during pesticide manufacture and application. Skin absorption can occur when dermal contact is made during handling and application of the insecticide, and when contact is made with chemical residues on plants, fruits, and foliage; in soil; and on dust particles after spraying. Some organophosphate insecticides (thiophosphates) are applied in the sulfur-containing (-thion) form but readily undergo desulfuration (removal of a sulfur atom from the molecule) to form a more toxic oxygen-containing (-oxon) form. In the field, this conversion occurs slowly under the influence of oxygen and light, often producing residues that are not only more toxic but more readily absorbed through the skin. The conversion can also occur during storage, making it important to promptly dispose of unused sulfur-containing pesticides.

Federal law prohibits field workers and structural pest control workers from entering a sprayed area without protective equipment until a specified interval of time has elapsed. Premature entry into sprayed fields or fumigated homes has caused acute organophosphate toxicity and death. Poisonings have occurred even when persons entered treated areas after the prescribed interval.

Although a few cases of chronic and mildly acute dietary poisonings have been reported, hazards to consumers from surface contamination of food appear to be minimal. If fruits and vegetables are thoroughly washed and the time elapsed between spraying and consumption is sufficient for insecticide degradation, pesticide poisoning is unlikely. However, some organophosphate and carbamate insecticides act systemically and can be translocated into foliage and fruit when applied at an improper time before harvest. Outbreaks of aldicarb intoxication, which affected hundreds of watermelon and cucumber consumers, occurred during the 1980s from misapplication of this systemic-acting insecticide.

Organophosphate and carbamate compounds, either alone or in combination with other insecticides, account for most pesticide-related poisonings. Poisonings have resulted from suicidal, homicidal, and accidental exposures. With improper storage, children, as well as adults, can mistake these chemicals for liquor, medicine, or other consumables. Pesticides usually contain solvent carriers such as toluene or xylene that are labeled as inert ingredients but may produce toxic effects in a pesticide ingestion. (The inert ingredients included on the labels of most pesticide containers refer to their application as a pesticide and not to their toxicologic activity.) Hence, the treatments suggested on pesticide container labels often are incomplete. Consumers should consult a physician or the regional poison control center if poisoning is suspected.

Who's at Risk

☐ **Farm workers, pesticide formulators and applicators, and their families are at greatest risk of exposure to pesticides.**

Seasonal or migrant farm workers (estimated 2.5 million), agricultural workers involved in the formulation and application of pesticides, and structural pest-control workers have the highest incidence of pesticide exposure. The improper use of pesticide containers as drinking or cooking utensils by field workers and their families and contamination of open water containers during aerial pesticide spraying have resulted in exposure. Other persons who may be exposed to organophosphates include workers in chemical manufacturing plants, truckers, longshoremen, chemical warfare (nerve gas) producers, and military personnel.

☐ **Proper precautions should be taken while mixing or applying insecticides because dermal absorption can be substantial and even lead to death.**

Despite extensive regulation, labeling, and educational efforts, the public remains unaware that fatal amounts of organophosphates can be absorbed through the skin. Because dermal absorption is so great, workers have been poisoned by wearing work clothes contaminated with these chemicals. Laundering may not be effective in removing some organophosphates; contaminated clothing may have to be burned, especially leather articles. Although the concentrations and toxicities of insecticides for home use are sometimes less than the concentrations and toxicities of the insecticides used in commercial agriculture, home gardeners should avoid all dermal contact and follow the label instructions carefully.

☐ **Children are at increased risk of exposure to pesticides and are more susceptible to their adverse health effects.**

Children can be exposed to pesticides by playing in areas where the chemicals have been sprayed, spilled, or improperly stored, and by playing with packages or instruments used in spraying. The mouthing and exploratory behaviors of young children and their tendency to play on the floor or ground increases their risk of exposure to pesticides or pesticide residues. Infants under 6 months of age have incompletely developed acetylcholinesterase systems and immature livers, and this may increase the susceptibility of young infants to cholinesterase-inhibiting pesticides.

Emergency personnel responding to pesticide spills, accidents, or poisonings are at risk not only of primary contamination but also of secondary contamination from contaminated persons and equipment. Appropriate protective clothing should be worn and care should be exercised during the decontamination of victims. In one case, the hospital emergency department staff were affected by xylene, which vaporized from the vomitus of a patient who had ingested a pesticide; the vomitus had been left in an open basin for an extended period of time.

Other persons who may be susceptible to the adverse effects of organophosphate pesticides include a small percentage of the population who have an atypical variant of plasma cholinesterase. This genetic abnormality decreases the amount of cholinesterase available and renders persons unusually sensitive to succinylcholine, a paralytic agent used in emergency intubations and abdominal surgeries. They may also be vulnerable to poisoning when cholinesterase activity is further depressed by insecticide exposure (although this has not been proven). Low plasma cholinesterase levels are also exhibited by long-distance runners; women in early pregnancy or using birth control pills; and persons who have advanced liver disease, chronic alcoholism, malnutrition, or dermatomyositis. Persons who have asthma and are exposed to organophosphate pesticides may be at increased risk because many of these compounds cause narrowing of the airways, which can exacerbate breathing difficulties.

Challenge

Additional information for the case study: During your conversation with the patient's brother, you learn that a spill occurred in the pesticide formulation area 2 days ago. The patient's brother had been mixing several chemicals, including an organophosphate insecticide, and spilled the mixture on the floor and on his clothes. After quickly removing his clothing, which consisted of rubber gloves, a cartridge respirator, a pair of coveralls kept in the formulation area, and his street clothes, he immediately showered. He cleaned the floor in the formulation area using a mixture of sand and other inert materials kept on hand for that purpose. He then buried the spilled contents. He took precautions to avoid contact with the chemicals during clean-up, and his wife laundered the coveralls separately from their other clothing. He saw no reason to mention the incident to his brother, who was on vacation at the time.

(1) What are the most likely routes of exposure for the patient in the case study?

(2) Who else could have been, or yet may be, at risk from this accident?

Biologic Fate

☐ **Organophosphate and carbamate insecticides can cause systemic poisoning when absorbed by any route.**

☐ **Thiophosphate insecticides may be converted in vivo and in the environment to an organophosphate that has greater skin penetration and clinical effects than the parent compound.**

Organophosphate and carbamate pesticides are absorbed readily by inhalation, ingestion, and skin absorption. The water solubility of some organophosphate and carbamate pesticides allows them to be absorbed by plants and also to act as systemic poisons in both insects and mammals. Because these compounds are distributed rapidly throughout the body, they typically are associated with rapid onset of symptoms, rarely longer than a few hours after a toxic exposure. However, the more lipid-soluble organophosphates, such as chlorfenthion and fenthion, can undergo initial lipid storage with subsequent redistribution and may not produce medical crisis for several days. Symptoms can persist for several weeks and periodic relapses can occur, requiring additional therapy.

In the body, as well as in the environment, some organophosphates can be converted from the -thion form to the more toxic -oxon form; rates of conversion vary widely but are more rapid in vivo than in the environment. In the body, conversion is brought about chiefly by hepatic microsomal esterases. Ultimately, both the -thion and -oxon forms are usually metabolized to alkyl phosphates and other products that are of relatively low toxicity and are excreted rapidly. Carbamates are also metabolized in the liver, and the products are excreted in urine without evidence of significant accumulation.

Physiologic Effects

Neurobehavioral Effects

☐ **Acetylcholinesterase, which is critical to control of nerve impulse transmission, is inhibited by organophosphate and carbamate pesticides.**

Organophosphate and carbamate compounds share a common pathophysiology—they combine with and thereby inhibit cholinesterase enzymes, of which acetylcholinesterase (AChE) in nerve tissue is the most important. Inactivation of AChE results in accumulation of acetylcholine at the neuroreceptor transmission site, resulting in massive overstimulation of the cholinergic system.

Initially, a weak reversible bond is formed between AChE and the organophosphate or carbamate pesticide. With time, however, a more permanent AChE-phosphate bond forms that inactivates the enzyme and requires an antidote to break. This process is known as "aging." If an antidote (pralidoxime [2-PAM]) is not given within 24 to 48 hours after most organophosphate exposures, the AChE-phosphate bond becomes so strong that physiologic recovery will depend on de-novo synthesis of AChE. At the nerve junction, AChE is restored in an average of 2 weeks; in the body as a whole, it may require 1 to 3 months to restore enzyme activity to near normal levels.

- ☐ **Because organophosphates may "age" in the body, antidote (pralidoxime) must be administered within 12 to 48 hours after exposure to be effective.**

Compared with the AChE-phosphate bond, the AChE-carbamate bond is relatively weak, and because the AChE-carbamate complex is inherently transient, aging does not occur. Therefore, carbamate pesticides produce an acute toxicity of much shorter duration than organophosphate pesticides and usually without persistent sequelae. Antidotes in the form of enzyme reactivators (pralidoxime) are rarely required treatment for carbamate poisonings because the formation of the AChE-carbamate complex is spontaneously reversible. However, the use of the atropine antidote is valuable even in carbamate poisonings, especially in cases where maintenance of airway and respiration is important.

Inhibition of AChE causes acetylcholine to accumulate at synaptic sites. The accumulation results initially in overstimulation and then in paralysis of neurochemical transmission. The character, degree, and duration of the resulting physiologic effects are directly related to the amount and rate of AChE enzyme inhibition at certain receptor sites in the central and peripheral nervous systems. Some critical mass of AChE must be inactivated before the signs and symptoms of poisoning manifest.

- ☐ **Several organophosphate pesticides can cause delayed peripheral neuropathy and chronic central neurotoxicity.**

Accumulation of acetylcholine in the brain causes sensory and behavioral disturbances, incoordination, depressed cognition, and respiratory failure (the usual cause of death). Other clinical manifestations are variable and depend on the balance of enzyme inhibition at cholinergic neuroeffector junctions (muscarinic effects) and at voluntary skeletal nerve-muscle junctions and autonomic ganglia (nicotinic effects) (Table 1). Organophosphate pesticides cause muscarinic, nicotinic, and central-nervous-system (CNS) effects, whereas carbamate pesticides cause predominantly muscarinic effects.

Table 1. Common manifestations of acetylcholinesterase inhibition by site

System	Receptor Type	Organ	Action	Manifestation
Parasympathetic	Muscarinic	**Eye**		
		Iris muscle	Contraction	Miosis
		Ciliary muscle	Contraction	Blurred vision
		Glands		
		Lacrimal	Secretion	Tearing
		Salivary	Secretion	Salivation
		Respiratory	Secretion	Bronchorrhea, rhinitis, pulmonary edema
		Gastrointestinal	Secretion	Nausea, vomiting, diarrhea
		Sweat	Secretion	Perspiration
Sympathetic (Sympatholytic)		**Heart**		
		Sinus node	Slowing	Bradycardia
		Atrioventricular (AV) node	Increased refractory period	Dysrhythmias, heart block
		Smooth muscle		
		Bronchial	Contraction	Bronchoconstriction
		Gastrointestinal wall	Contraction	Vomiting, cramps, diarrhea
		Sphincter	Relaxation	Fecal incontinence
		Bladder		
		Fundus	Contraction	Urination
		Sphincter	Relaxation	Urinary incontinence
Neuromuscular	Nicotinic	**Skeletal**	Excitation	Fasciculations, cramps, followed by weakness, pupillary dilation, loss of reflexes, paralysis
		Heart	Excitation	Tachycardia
Central nervous		**Brain/Brainstem**	Excitation (early)	Headache, malaise, dizziness, confusion, manic or bizarre behavior
			Depression (late)	Depression, then loss of consciousness; respiratory depression; diaphragm paralysis

Adapted from LaDou J, ed. Occupational Medicine. Norwalk, Connecticut: Appleton and Lange, 1990:412.

Delayed Neuropathy

Symmetric distal axonal degeneration is a systemic health effect caused by some organophosphate pesticides that is not due to AChE inhibition. The degeneration is a "dying back" of large diameter axons and their myelinic sheaths in distal parts of the peripheral nerves and in long spinal-cord tracts. Studies indicate the degeneration is caused by inhibition of a neuronal, nonspecific carboxylesterase known as neuropathic target esterase, which appears to have a role in lipid metabolism in neurons.

The resulting clinical syndrome, organophosphate-induced distal neuropathy (OPIDN), typically begins about 7 to 14 days after treatment, after other signs of organophosphate poisoning have improved or resolved. These late neuropathies are primarily distal and sensorimotor in nature; predominant overall presentation is that of a motor disorder. Usual manifestations are flaccidity or paralysis and paresthesia of the extremities, predominantly the legs. (Foot drop, spasticity, and hyperactive reflexes are not uncommon.) In severe cases, paralysis can extend to involve the hands and muscles of the forearms and may mimic Guillain-Barré syndrome.

Only some organophosphate compounds (e.g., Trichlorphon, Merphos, triorthocresyl phosphate [TOCP], and triorthotolyl phosphate [TOTP]) have been associated with delayed neuropathy in humans, and no carbamate compounds have been reported to cause this condition. During the Depression of the 1930s, thousands of people in the United States fell victim to "ginger jake paralysis," a condition caused by drinking an alcoholic extract of Jamaican ginger that had been adulterated with TOTP, a compound used as a plasticizer and as an additive in aviation fuels and lubricants. In 1959, several thousand people in Morocco were poisoned when jet fuel containing TOCP was mixed with olive oil and sold as cooking oil. Effects of these ingestions, which commonly included calf pain and tingling in the hands and feet initially, persisted for weeks to years.

Another syndrome of delayed onset neuropathy has recently been described by clinicians in Sri Lanka in conjunction with suicide attempts involving organophosphate insecticides. This paralytic condition, known as "intermediate syndrome," consists of a sequence of neurologic signs that appear 24 to 96 hours after acute cholinergic crisis but before the expected onset of OPIDN. The major effects are weakness of proximal limb muscles, neck flexors, and respiratory muscles. Cranial nerve palsies are common. Knee and ankle reflexes may be absent. Unlike OPIDN, this sequence does not cause sensory impairment. Risk of death during this time interval is considerable, however, because of respiratory depression and distress.

Other Effects

☐ **Organophosphate and carbamate pesticides are primary skin irritants.**

Dermal lesions are more common than systemic poisonings among persons who encounter pesticides in the course of their occupational activities. About one-third of all reported pesticide-related diseases are dermatologic. Many organophosphate and carbamate pesticides cause primary irritant dermatitis; only a few are known to cause allergic contact dermatitis (e.g., parathion, malathion, and dichlorvos), and some can trigger phototoxic dermatitis (see *Case Studies in Environmental Medicine: Skin Lesions and Environmental Exposures*). Because pesticides are often used in combination, it can be difficult to identify the pesticide causing the problem.

☐ **Some cholinesterase-inhibiting pesticides are suspected animal or human carcinogens; some have been found to cause developmental effects in experimental animals.**

Results of experimental animal studies and human epidemiologic studies suggest an association between certain organophosphate compounds and cancer. A proposed mechanism of action is altered cellular immunity. However, the cholinesterase-inhibiting compounds commonly used as insecticides have not been found to be carcinogenic.

Some organophosphate compounds caused reduced rates of conception, reduced fertility, and adverse developmental effects in rats. However, other species of experimental animals showed no reproductive or teratogenic effects from parathion. No evidence exists that cholinesterase-inhibiting insecticides are significant teratogenic risks to humans.

Challenge

(3) Are the signs and symptoms exhibited by the patient in the case study consistent with poisoning by an organophosphate pesticide? Explain.

(4) Would you treat the patient differently if he had been exposed to a carbamate rather than an organophosphate pesticide? Explain.

Clinical Evaluation

The relative intensity of clinical manifestations in patients poisoned by organophosphate or carbamate pesticides is strongly influenced by (1) the toxicity and route of absorption of the pesticide, and (2) the degree and rate of AChE inhibition with subsequent accumulation of acetylcholine.

History and Physical Examination

Diagnosis of organophosphate or carbamate toxicity is based on the history of exposure and the presence of characteristic muscarinic, nicotinic, and CNS manifestations. In suspected organophosphate poisoning, the physical examination should include careful evaluation of the cardiovascular system and the nervous system. The medical history should emphasize the following elements:

- Occupational history (particularly involving exposures to insecticides)
- Residence: age, pest control programs (both structural and grounds), and location in relation to certain industrial facilities (sites where pesticides and related products are produced or stored)
- Twenty-four hour recall of all foods and liquids ingested
- Hobbies: management of playing fields, gardening
- Medications, such as pilocarpine for glaucoma

(See *Case Studies in Environmental Medicine: Taking an Exposure History.*)

Signs and Symptoms

Acute Exposure

Because clinical manifestations are typical, patients who are severely ill from acute pesticide exposure seldom present a diagnostic challenge if the history of exposure is also available. Miosis, fasciculations, excess secretions, and hyperactive bowels constitute a classic presentation of organophosphate poisoning. Often a petrochemical-like odor emanates from the patient's breath or clothing.

☐ **The onset of symptoms of acute organophosphate or carbamate poisoning usually occurs shortly after exposure but can be delayed up to 12 hours.**

Depending on the route of exposure, symptoms of acute organophosphate and carbamate poisoning usually develop within 4 hours of contact, but may be delayed for up to 12 hours. Initial symptoms may be headache, dizziness, nausea, and abdominal pain. Signs of

- ☐ **Respiratory failure is the usual cause of death after acute poisoning by cholinesterase-inhibiting pesticides.**

severe poisoning may include coma, pulmonary edema, ataxia, toxic psychosis (manifested as confusion or bizarre behavior), dyspnea, fasciculations, bradycardia, cardiac dysrhythmias, and weakness or paralysis. The actual cholinergic symptomatology may depend somewhat on the route of exposure and the balance between nicotinic (organophosphate pesticides) and muscarinic receptors (organophosphate and carbamate pesticides). (See Table 1, page 8.) The symptoms of carbamate poisoning typically are less severe and of shorter duration than those of organophosphate poisoning.

Chronic Exposure

Poisoning due to chronic exposure to cholinesterase-inhibiting insecticides may not be readily apparent because the symptoms are sometimes nonspecific and resemble other illnesses such as influenza, heat exhaustion, alcohol toxicity, or simple fatigue. Also the history of exposure may not be particularly remarkable in such cases. Repeated absorption of organophosphates at subacute concentrations may cause persistent anorexia, weakness, and malaise ("orange-picker's flu"), a condition seen in farm workers engaged in crop spraying. Certain neurobehavioral effects may persist after chronic exposure, as well as after acute toxicoses.

Despite the lack of distinct symptomatology, it is important to aggressively investigate all suspected cases of chronic pesticide poisoning because such a case may represent a sentinel event, indicating a workplace hazard or other populations at risk. In some states, failure to report a pesticide-related illness can result in a fine. (Check with your state health department.)

Laboratory Tests

A combination of history, physical examination, and laboratory tests will provide the most appropriate approach to diagnosing pesticide-related illnesses.

Direct Biologic Indicators

- ☐ **Analysis of blood and urine for direct evidence of organophosphate or carbamate exposure is valuable, but usually is available only from reference laboratories.**

Detection of intact organophosphate or carbamate compounds in blood is usually not possible except during or soon after exposure. In general, cholinesterase-inhibiting pesticides do not remain unhydrolyzed in the blood more than a few minutes or hours, unless the quantity absorbed is large or the hydrolyzing liver enzymes are inhibited.

The metabolites of organophosphates (i.e., the corresponding alkyl phosphates) and the unique metabolites of N-methyl carbamates can often be detected in the urine up to 48 hours after exposure. The appearance of these urinary metabolites can demonstrate pesticide absorption at lower dosages than those required to depress cholinesterase activity and at much lower dosages than those required to produce signs and symptoms. However, testing for these excretion products generally is available only from reference laboratories, and the results may be delayed because of the complexity of the analyses.

Indirect Biologic Indicators

☐ **Measurement of red blood cell or plasma cholinesterase activity can help to confirm exposure to an organophosphate or carbamate pesticide.**

Determination of cholinesterase activity is useful in routine biologic monitoring of workers chronically exposed to cholinesterase-inhibiting pesticides, as well as in diagnosing acute poisoning. Cholinesterase depression is usually apparent within a few minutes or hours after significant absorption.

Acetylcholinesterase enzymes measured in red blood cells (RBC) (referred to as true cholinesterase) and in plasma or serum (referred to as pseudocholinesterase) are actually surrogate indicators for activity occurring at neuroreceptor sites. Both plasma and RBC cholinesterase should be determined on each sample because the two tests have different meanings, and the results must be considered in combination for proper interpretation.

Plasma cholinesterase is more labile than RBC cholinesterase and is therefore less reliable in reflecting actual depression of enzyme activity at neuroeffector sites. Plasma cholinesterase is generally more rapidly inactivated by exposure to organophosphates, and it may also be slightly depressed by factors such as infection, alcohol, hepatic disease, birth control pills, and pregnancy. Because plasma cholinesterase is produced in the liver, it can be regenerated quickly.

RBC cholinesterase is the same enzyme as that found in the nervous system. It is depressed more slowly than plasma cholinesterase, but because the depression is more specifically attributable to organophosphates, its level more accurately reflects the degree of actual enzyme inactivation at neuroeffector sites. RBC cholinesterase activity is generally restored only as new red blood cells are formed. (Regeneration of red blood cells takes place at a rate of about 1% per day.) RBC cholinesterase activity is slightly affected by certain rare conditions that damage the cell membrane, such as hemolytic anemias or other causes of reticulocytosis. (Hemolytic anemias will cause a relatively elevated level of plasma cholinesterase but a lowered RBC cholinesterase as the cholinesterase of the lysed cells is liberated into the plasma.)

It is difficult to interpret cholinesterase inhibition without baseline values because normal human cholinesterase levels vary widely. The laboratory normal range is not useful because upper and lower limits of normal range may differ by a factor of 4 with some common laboratory methods. Inhibitions of from 25% to 50% of the individual's baseline enzyme activity are generally regarded as evidence of toxicity. However, in both acute and chronic exposures, clinical symptoms have been absent even when cholinesterase levels were inhibited by 50% of baseline. The development of signs and symptoms is related to both the rate of decline in enzyme activity and the absolute level of enzyme activity.

Because of marked variation among different methods of analysis and among laboratories using the same method, cholinesterase tests, including baseline determinations and serial follow-up testing, should be performed by the same laboratory, using the same method. It is misleading to extrapolate from one method to another or from one laboratory's results to another's. A laboratory performing cholinesterase tests should have a rigorous quality-control program and an accurate and reproducible method of analysis.

Other laboratory evaluations for patients seriously exposed to organophosphate or carbamate pesticides may include CBC and determinations of electrolytes, glucose, BUN, creatinine, and liver enzymes. Arterial blood gases and chest radiography are useful in cases of inhalation exposure or respiratory compromise.

Challenge

(5) What is the differential diagnosis for the patient in the case study?

(6) What laboratory tests will you request?

(7) The patient has an initial RBC cholinesterase that is 25% of the laboratory's normal value. What factors, other than organophosphate poisoning, could account for this dramatic depression of RBC cholinesterase?

Treatment and Management

Organophosphate poisoning is one of the few cases of acute toxicity for which specific antidotes are available. The severity of the poisoning, among other considerations, should dictate the institution of the management procedures. **If a patient has been poisoned by organophosphate exposure, decontamination should proceed concurrently with resuscitative and antidotal measures.**

☐ **Nicotinic and muscarinic effects of acute pesticide poisoning require immediate, aggressive emergency management.**

Protective clothing (including rubber gloves) should be worn when decontaminating patients exposed to organophosphate compounds. If patients are able and cooperative, they may assist with their own decontamination. Remove clothing and personal belongings and double-bag them. Clothing and leather items are difficult to decontaminate, and in most cases, should be incinerated.

Flush exposed skin and hair with plain water for 2 to 3 minutes (preferably under a shower), then wash twice with mild soap. Be certain to clean under fingernails and in all skin folds. Rinse thoroughly with water. If the patient's eyes were exposed, irrigate them with plain water or saline for 5 minutes; remove contact lenses if present.

☐ **Atropine is the primary antidote for adverse muscarinic effects.**

In cases of ingestion, gastric lavage is preferred over emesis because CNS depression may develop rapidly. The effectiveness of lavage, however, diminishes rapidly with time. The airway must be vigorously protected from aspiration of gastric contents. A slurry of activated charcoal with a cathartic (sorbitol, magnesium sulfate or citrate) should be administered even though most organophosphate compounds are not efficiently adsorbed to charcoal.

☐ **Pralidoxime (2-PAM) is the antidote of choice to control nicotinic manifestations in organophosphate poisoning.**

The recommended treatment for serious poisoning is as follows:

(a) Establish a clear airway by aspiration of secretions. If necessary, intubate the patient and consider mechanical means to assist respiration. **(Atropine, which is recommended in the next step, can cause ventricular fibrillation when administered to an hypoxic patient.)**

(b) Intravenously administer atropine sulfate (adult: 2-4 milligrams [mg]; <12 years: 0.05 mg/kilogram [kg] body weight) and repeat at 3- to 10-minute intervals until signs of atropinization appear (e.g., reversal of excess salivation, bronchial secretions, and sweating). Maintain atropinization by repeated dosage for at least 24 hours; total doses up to 50 mg/day have been given. (In one reported case, 1000 mg/day was given.)

Atropine controls muscarinic manifestations but has no effect on nicotinic or CNS manifestations. Severely poisoned patients may exhibit remarkable tolerance to atropine and massive amounts may be required. Reversal of muscarinic signs and symptoms, not an arbitrary dose limit, is the endpoint. If signs of atropine toxicity (fever, muscle fibrillations, and delirium) appear, atropine administration should be discontinued temporarily while the severity of poisoning is reevaluated. The clinician inexperienced in handling patients poisoned by cholinesterase-inhibiting pesticides should contact a regional poison control center or a medical toxicologist for specific guidelines before giving further treatment.

(c) Obtain a blood sample (heparinized) for cholinesterase determination. (The blood sample should be taken before administering the antidote pralidoxime chloride [2-PAM, Protopam] recommended in the next step because this antidote quickly reactivates the enzyme.)

(d) If the patient exhibits muscle weakness, twitching, or respiratory depression, administer 2-PAM intravenously, preferably as an infusion in 100 mL of saline over a 15- to 30-minute period (adult: 1-2 grams [gm]; <12 years: 20-50 mg/kg body weight). Rapid injection of 2-PAM can cause tachycardia, laryngeal spasm, muscle rigidity, and transient neuromuscular blockage.

Pralidoxime is an oxime that breaks the bond in the AChE-phosphate complex and should be used for most clinically significant organophosphate poisonings. However, in certain carbamate poisonings (e.g., carbaryl) 2-PAM is generally of limited value and may be hazardous. If a combination of carbamate and organophosphate poisoning has occurred, or if the pesticide cannot be identified, 2-PAM should be administered.

Administer 2-PAM as soon as possible but within 48 hours after organophosphate exposure. Beyond this time, AChE can become firmly bound to the phosphate in an "aging" process, which results in the enzyme becoming refractory to reactivation.

(e) Repeat the dosage of 2-PAM in 1 to 2 hours, then at 10- to 12-hour intervals, if needed. If testing is readily available, the RBC and plasma cholinesterase activity of the patient can be monitored to determine the effect of 2-PAM.

(f) Observe the patient closely for at least 72 hours for recurrence of toxicity. Monitor pulmonary ventilation and cardiac status, and administer symptomatic treatment as required. If convulsions occur despite atropine and 2-PAM therapy, diazepam or other anticonvulsants may be administered. Slowly administer the anticonvulsant intravenously, while watching for hypotension and hypoventilation.

Medications that may be contraindicated in organophosphate or carbamate pesticide poisoning include morphine, aminophylline, and phenothiazines because they have weak anti-cholinesterase activity. However, they are not contraindicated unequivocally and should be administered if there are other extenuating medical reasons for their use.

(g) Notify the health department of all pesticide exposures resulting in poisoning. Patients should not return to an environment where further exposure is possible until their blood cholinesterase activity has reached a recommended minimum (typically 80% of the baseline level). Neither atropine nor 2-PAM should be administered prophylactically to workers or others exposed to organophosphates or carbamates. Oral atropine should not be used in treating pesticide poisonings.

Challenge

(8) What agents would be contraindicated for the patient in the case study?

(9) Why should atropine or 2-PAM not be used prophylactically?

(10) Describe the probable course and outcome for this patient.

Standards and Regulations

The U.S. Environmental Protection Agency (EPA) was given wide-ranging authority over domestic pesticide usage by regulations contained in the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), passed in 1947 and amended in 1972 and 1988. EPA is responsible for registering all pesticides for use in the United States, establishing guidelines for registration procedures, certifying individual state programs for licensing pesticide applicators, establishing reentry intervals, specifying label information and use instruction, and setting acceptable tolerance levels in food and water.

Workplace

The Occupational Safety and Health Administration (OSHA) mandates permissible exposure limits (PELs) for pesticides in the workplace. PELs for organophosphate pesticides are typically time-weighted averages for an 8-hour workshift and range from 0.05 mg/cubic meters (m^3) of air to 15.0 mg/m^3. PELs depend on the pesticide's toxicity, which is determined by the LD_{50} (lethal dose to 50% of the test animals exposed to a chemical administered in a single dose by any route other than inhalation) value and other hazard indicators such as corrosiveness, dermal rating, and carcinogenicity.

Environment

Water

The enforceable maximum contaminant level (MCL) set by EPA for drinking water varies for each pesticide. The EPA Drinking Water Hotline ([800] 426-4791) and Office of Pesticide Programs ([703] 557-2440) can provide information on specific pesticide regulations.

Food

EPA, in conjunction with the Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA), monitors and regulates pesticide residues and their breakdown products in food. Established tolerance limits for most cholinesterase-inhibiting pesticides and their metabolites in various raw agricultural commodities range from 0.05 parts per million (ppm) to 10 ppm.

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Sources of Information

More information on treating and managing patients exposed to cholinesterase-inhibiting pesticides can be obtained from ATSDR, the National Pesticide Telecommunications Network (24-hour hotline, [800] 858-7378), your state and local health departments, the plant division of your state's department of agriculture, county agricultural commissioner and cooperative extension agents, and university medical centers. *Case Studies in Environmental Medicine: Cholinesterase-Inhibiting Pesticide Toxicity* is one of a series. To obtain other publications in this series, please use the order form on the inside back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of the Director, at (404) 639-6204.

Answers to Pretest and Challenge Questions

Pretest questions are on page 1. Challenge questions begin on page 5.

Pretest

(a) The patient's problem list includes headache, dizziness, nausea, vomiting, hypersalivation, diaphoresis, miosis, altered mental status, paralysis, fasciculations, and autonomic dysfunction.

The differential diagnosis might include the following:
organophosphate or carbamate poisoning
heroin/opiate overdose
phenothiazine overdose
pontine tumor or subarachnoid hemorrhage
CNS infection, such as encephalitis, meningitis, or brain abscess
botulism, gastroenteritis
congestive heart failure
heat exhaustion
alcohol toxicosis

(b) The history provided by the patient's brother and the signs and symptoms are consistent with poisoning due to a cholinesterase-inhibiting pesticide (see Challenge answer 3). It is important to discover the route of exposure so that future exposures can be prevented. (See Challenge question and answer 1.) Further questioning may reveal whether the pesticide was an organophosphate or carbamate. You should also query the brother and other family members about the patient's liquid and food consumption for the past 24 hours and medications that he may be taking.

(c) Laboratory confirmation of organophosphate poisoning can be sought by measuring the activities of RBC and plasma cholinesterase—both enzymes are affected by organophosphates. Although individual normal values vary markedly, poisoning is considered to have occurred when cholinesterase activity is 25% to 50% of normal. However, not only is the degree of cholinesterase depression important, but the rate of depression is also pertinent. A repeat acetylcholinesterase test should be performed in 2 to 3 weeks to determine whether the value has increased significantly.

(d) The treatment that resulted in the patient's remarkable recovery included the administration of atropine and 2-PAM.

Challenge

(1) The most likely routes of exposure for the patient are inhalation and dermal contact. The brothers apparently wore adequate protective equipment, and they have performed the pesticide mixing operations many times without ill effects. It is significant that only one of the men became ill. A possibility exists that the illness is related to the pesticide spill in the formulating area.

Using investigative results by the State Department of Agriculture and by the process of eliminating other conditions, such as a loose cartridge respirator, you conclude that contamination most likely occurred via the coveralls that had been worn during the spill.

(2) Anyone wearing the coveralls may be similarly exposed. Laundering, even multiple washings, may not completely remove some pesticides. In the process of laundering, the coveralls could also contaminate the clothing of other family members. The coveralls should be burned.

(3) Yes. The patient manifests the classic signs and symptoms of organophosphate poisoning. The effects can be classified into three categories: muscarinic or hollow-organ parasympathetic manifestations, nicotinic or autonomic ganglion and somatic motor effects, and CNS effects. Carbamate poisoning can be distinguished from organophosphate poisoning by the absence of nicotinic effects. Carbamate poisoning is also immediately reversible by a small dose of atropine, compared with the large doses of atropine needed in organophosphate intoxications.

The muscarinic effects involve the bronchial tree, sweat and lacrimal glands, heart, pupils, and ciliary body. Muscarinic effects are easily remembered by the acronym SLUDGE—salivation, lacrimation, urination, defecation, gastrointestinal distress, and emesis.

Nicotinic effects typically include muscle fasciculations, cramping, and weakness that can progress to paralysis, areflexia, hypertension, tachycardia, pupillary dilation, and pallor. Respiratory failure may occur secondary to weakness of the pulmonary muscles or paralysis of the diaphragm. Hypertension and pupillary dilation have also been noted.

CNS effects may include restlessness, emotional lability, headache, tremor, drowsiness, delirium, psychosis, coma, and cardiorespiratory depression.

(4) Yes, if the patient had been exposed to a carbamate, administration of 2-PAM to reactivate the AChE from the AChE-carbamate complex would usually be unnecessary because the carbamate complex is spontaneously reversible. Recovery from carbamate poisoning is typically more rapid than from organophosphate poisoning and without persistent sequelae.

(5) See Pretest answer (a) above.

(6) See Pretest answer (c) above.

(7) Diet, medications, and reticulocytosis may lower the RBC acetylcholinesterase activity. Reticulocytosis may be the result of recovery from hemorrhage, hemolysis, liver disease, jaundice, hepatitis, pregnancy, and pernicious anemia or other anemias. However, these conditions cannot account for the severe lowering of the RBC cholinesterase activity seen in this patient. (The RBC cholinesterase activity is 25% of normal.)

(8) Drugs that are contraindicated for nearly all organophosphate-poisoned patients include opiates and phenothiazines; they may increase the risk of cardiac dysrhythmias. A small portion of the population possess a genetic variant of plasma cholinesterase that can cause death if succinylcholine is administered to the patient.

(9) Atropine and 2-PAM should not be administered prophylactically because they cause blurred vision and lack of sweating. The loss of sweating may cause hyperthermia under certain conditions. Administration of antidote can mask signs and symptoms of pesticide poisoning, thus allowing dangerously prolonged exposure.

(10) After 4 weeks, the patient shows no sign of delayed neuropathy or other adverse effects. The prognosis is, therefore, excellent. Chronic effects similar to cerebral dysfunction have been noted in some patients acutely poisoned.

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Preliminary Communication

INFERTILITY IN MALE PESTICIDE WORKERS

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Summary A number of cases of infertility were discovered among men working in a California pesticide factory. The suspected cause was exposure to the chemical 1,2-dibromo-3-chloropropane (D.B.C.P.). The major effects, seen in 14 of 25 non-vasectomised men, were azoospermia or oligospermia and raised serum-levels of follicle-stimulating hormone and luteinising hormone. No other major abnormalities were detected, and testosterone levels were normal. Although a quantitative estimation of exposure could not be obtained, the observed effects appeared to be related to duration of exposure to D.B.C.P.

INTRODUCTION

MALE infertility can result from pathological pro-

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COMPARISON OF NON-VASECTOMISED D.B.C.P. WORKERS WITH VERY LOW (GROUP A) AND NORMAL (GROUP B) SPERM-COUNTS*

Group	No. of subjects	Age (yr)	Exposure (yr)	Sperm-count (×10⁶/ml)	F.S.H. (mI.U./ml)	L.H. (mI.U./ml)	Testosterone (ng/dl)
A	11	32·7±1·6†	8·0 ±1·2‡	0·2±0·1§	11·3±1·8‡	28·4±3·3†	459±35
B	11	26·7±1·2†	0·08±0·02‡	93±18	2·6±0·4‡	14·0±2·8†	463±31

*All results given as mean ± standard error of mean.

†Difference between groups A and B significant at $P<0.01$.

‡Difference between groups A and B significant at $P<0.001$.

§9 workers with 0 sperm/ml, 2 with 1×10^6/ml.

cesses affecting production or transport of sperm. Infection, trauma, varicocele, cryptorchidism, exposure to toxic agents, and autoimmunity have all been cited as causes of male infertility, but in many cases the cause is unknown.[1]

We have investigated infertility observed in a group of men working in a California pesticide factory. Although the connection has not been proved beyond doubt, the cause in these cases seems to be exposure to the nematocide, 1,2-dibromo-3-chloropropane (D.B.C.P.).

BACKGROUND

The company employing the affected men manufactures fertilisers and ammonia, and it formulates pesticides for agricultural and household use. In the latter process, workers mix, dilute, and repackage technical-grade pesticides obtained from primary chemical manufacturers. Some 100 different chemicals are used in the formulation of approximately 200 different products, including organophosphorus compounds, halogenated hydrocarbons, and carbamates. The products manufactured or formulated vary with market demand. Since 1962 the company has regularly formulated D.B.C.P. in a special agricultural chemical division (A.C.D.). For several years before the infertility was brought to our attention men working in the A.C.D. had become increasingly aware that few of them had recently fathered children. After a preliminary evaluation of 5 men had revealed oligospermia or azoospermia, other male employees were studied in more detail.

METHODS

Subjects

All 39 employees in the A.C.D. took part in the study. There were 3 supervisors, 24 production workers, 4 maintenance mechanics, 2 clerks, and 6 laboratory workers. 36 of the group were men, 11 of whom had had vasectomies. There was no way of determining exact differences in chemical exposure received by the production workers, since they were assigned interchangeably to different tasks. Thus, only the length of time they had worked in the A.C.D. could be used as a measure of exposure.

Procedure

Each of the 39 employees was asked to complete a medical-history questionnaire, and one of us (D.W.) then asked each subject specific questions about his or her reproductive system. All participants were also examined thoroughly.

Semen samples were obtained from all non-vasectomised men and were promptly taken to the laboratory for determination of sperm-count, motility, and morphology. Other laboratory tests done on all 39 subjects included urinalysis, complete and differential blood counts, blood chemistry, T3-resin uptake, and assays for serum-levels of thyroxine, testosterone, follicle stimulating hormone (F.S.H.), and luteinising hormone (L.H.). The last four tests were done by radioimmunoassay. All the analyses were performed by the clinical and endocrine laboratories of Alta Bates Hospital.

Early in the investigation it became apparent that infertility was associated with length of time worked in the A.C.D. To examine the relationship between exposure duration and sperm-count, we first excluded from our original group 3 women, 11 vasectomised men, and 3 men with sperm-counts between 10 million and 30 million. This left 11 men with indisputably low sperm-counts (≤1 million, group A) and 11 men with normal sperm-counts (≥40 million, group B). We then compared these two groups by age, time worked in the A.C.D., and serum L.H., F.S.H., and testosterone levels. After the preliminary evaluations, bilateral open testicular biopsies were performed on 9 volunteers representing a spectrum of chemical-exposure times and sperm-counts within the A.C.D.

RESULTS

None of the 3 women had had abnormal menstrual cycles, and all had borne children. None of the men had loss of libido, difficulty with erection or ejaculation, loss or altered distribution of facial or body hair, testicular atrophy, epididymal abnormalities, gynæcomastia, or abnormalities of the prostate. 3 had varicoceles, but all 3 had previously fathered children. 7 of the 36 men had never fathered children.

Some of the production workers had occasional symptoms, such as mild headache, nausea, light-headedness, and weakness, when formulating some organophosphorus pesticides. Symptoms due to irritation of the upper respiratory tract were also mentioned by some as being associated with their work in the manufacture of certain thiocarbamate compounds. No other important information was brought to light by the history or physical examination of any of the subjects. The few hepatic, renal, hæmopoietic, and thyroid abnormalities revealed by laboratory studies were consistent with previous medical problems.

The relationship of length of chemical exposure (time of employment) to sperm-count was striking (see table). Workers with sperm counts ≤1 million had been exposed at least three years. None with sperm-counts above 40 million had been exposed for more than three months.

The 2 men in group A (see table) who were not azoospermic showed great reduction of sperm motility and increases in abnormal forms. Sperm motility and morphology were normal in all the men in group B. The mean age in group A was slightly higher than in group B, but differences in testicular function would not be expected to result from this small age difference.

The mean level of F.S.H. was significantly higher in group A—a finding consistent with the severe impairment in spermatogenesis in these individuals.[1,2] F.S.H. levels in group B were in a range comparable with those in a larger, unexposed population of male employees from elsewhere in the company who are now being studied. Group A also had a higher mean L.H. level. This also probably represents a response to testicular damage, although serum-testosterone levels were comparable in the two groups. Thus, the stimulus for the increase in L.H. is not known. Studies are planned to evaluate testicular and pituitary hormone production in these workers.

The 2 women workers not currently using oral contraceptives had normal F.S.H. and L.H. results.

Preliminary evaluation of the testicular-biopsy results of the severely affected men indicated loss of spermatogonia, with no evidence of inflammation or severe fibrosis.

The 3 men not included in the comparison who had sperm-counts of 10 million–30 million had exposures between one and three years—an observation that supports the notion of a direct relationship between length of exposure and degree of oligospermia.

DISCUSSION

Chemically reduced male infertility related to occupation has seldom been reported. Lancranjan et al.[3] reported that lead-poisoned workers had lowered sperm-counts, decreased sperm motility, and a higher proportion of abnormal forms. Diminished libido and difficulty in erection and ejaculation were also found. Kepone, an organochlorine insecticide, severely poisoned workers in Virginia in 1975. Most of the affected workers had severe neurological abnormalities, and some were also reported to be infertile.[4]

The chemical suspected in the present investigation to be the cause of infertility had previously been shown to produce sterility in animals. D.B.C.P. was shown by Torkelson et al.[5] to be toxic to the testes of rats, guineapigs, and rabbits. In the rat testis it caused degeneration of the seminiferous tubules, increase in Sertoli cells, reduced sperm-count, and abnormal sperm morphology. Rats with these effects also showed hepatic and renal degeneration. D.B.C.P. was found to produce these changes through skin absorption as well as ingestion or inhalation. Faidysh et al.[6] showed that D.B.C.P. damaged the testes, liver, and kidneys of rats, but these organs regenerated in the survivors.

Airborne concentrations of D.B.C.P. in the factory we investigated are believed to be lower than the 1 p.p.m. limit recommended by Torkelson et al.[5] D.B.C.P. levels measured in early 1977 in the A.C.D. were 0·4 p.p.m. (averaged for an eight-hour day). These measurements were made with personal air-sampling devices.[7]

Research is being continued at this plant, together with studies in other areas. Follow-up studies of the affected workers are being planned. Our findings have raised a number of important issues. One is the significance of duration and intensity of exposure. Although all severely affected workers (group A) were, or had been, production workers for at least three years, the shortest time of exposure associated with oligospermia was only one year. Another question is whether the observed sterility is reversible in man as it has been shown to be in animals. Finally, since D.B.C.P. is carcinogenic in animals[8] and mutagenic in bacterial systems,[9] the possibility of such damage in man must also be considered seriously.

How big a problem D.B.C.P.-induced infertility is we do not yet know, but our communications with medical officers of other companies manufacturing D.B.C.P. clearly indicate that it extends beyond the formulating plant described here.

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Pesticide Food Poisoning from Contaminated Watermelons in California, 1985

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ABSTRACT. Aldicarb, a carbamate pesticide, is the most potent pesticide in the market and has a LD$_{50}$ of 1 mg/kg. In the United States it is illegal to use aldicarb on certain crops, e.g., watermelons, because it is incorporated into the flesh of the fruit. Once an accidental or illegal use of such a potent pesticide occurs, there is no easy way for the agricultural or public health system to protect the populace. This paper describes the impact of one such event upon the health of individuals and the institutions of California. On July 4, 1985, California and other western states experienced the largest known outbreak of food-borne pesticide illness ever to occur in North America. This was attributed to watermelons contaminated through the illegal or accidental use of aldicarb by a few farmers in one part of the state. Within California, a total of 1 376 illnesses resulting from consumption of watermelons was reported to the California Department of Health Services (CDHS). Of the 1 376 illnesses, 77% were classified as being probable or possible carbamate illnesses. Many of the case reports involved multiple illnesses associated with the same melon among unrelated individuals. Seventeen individuals required hospitalization. There were 47 reports of illness

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involving pregnant women, two of whom reported having subsequent stillbirths. Thirty-five of the remaining pregnant women were followed–up 9 mo after the epidemic; no additional stillbirths were found. To control the epidemic, it was necessary to embargo on July 4 and to destroy all watermelons in the state on July 7 and to effect a field certification program. The epidemic and the costly resultant control measures illustrate the difficulties in assuring the safe use of the most potent pesticide. The use of pesticides is controlled by an elaborate set of crop specific regulations. State and federal regulators use laboratory tests of produce samples to insure that regulations are followed. When inadvertent or illegal applications of pesticide occur in a particular crop, there is no system that guarantees that the public will not be exposed. For most pesticides, the effects may not be dramatic, but when a potent pesticide appears in a widely eaten commodity, the impact on health and the institutions that are designed to protect it can be devastating. This paper describes the course of one such event.

ON JULY 3, 1985, the Oregon Department of Health notified the California Department of Health Services (CDHS) of several cases of possible pesticide illness related to consumption of watermelons that were thought to have been grown in Arizona.[1,2] At 4:00 A.M. on July 4, a 62-y-old woman on digoxin therapy was treated at a Lake County, California, emergency department for hypotension, severe bradycardia (31 beats per minute [bpm]), atrial fibrillation, diaphoresis, vomiting, diarrhea, lacrimation, salivation, and muscle twitching. She had eaten watermelon about 30 min earlier. Her symptoms resolved following treatment with atropine. Two other family members who had consumed the same watermelon were also ill and had similar though milder symptoms. The treating physician notified the San Francisco Bay Area Regional Poison Control Center, which subsequently notified CDHS.

Later on the morning of July 4, Oregon officials reported to CDHS that aldicarb sulfoxide (ASO), a toxic degradation product of aldicarb, had been detected in several of the melons related to illness episodes in that state and that the origin of the melons was, in fact, from California.[1,2] Aldicarb, CAS No. 116-06-3, is a cholinesterase-inhibiting carbamate pesticide that is not registered for use on watermelons in the U.S. but commonly used on citrus, cotton, potatoes, peanuts, and soybeans. Within 2 h, calls to 10 California poison control centers, 20 selected emergency departments, and 1 county health department had identified an additional 12 presumed cases of pesticide illness related to consumption of watermelons. This included a group of 4 individuals in Bakersfield who had eaten a striped melon purchased at a roadside stand, a group of 6 individuals who had eaten a striped melon from a Los Angeles-area supermarket warehouse, and 2 individuals in the San Francisco Bay Area who had eaten green melons purchased at different retail stores. These illnesses were investigated by state and local health officials, and arrangements were made for obtaining watermelon samples.

Just prior to noon on July 4, statewide media advisories were issued that warned against eating watermelons, and an embargo was placed on the sale of watermelons throughout California. Usual product recall mechanisms were inoperative because the day was a national holiday. By late afternoon on July 4, case investigations and tracking of sources of melons back through the distribution chains had implicated a single Kern County shipper in several, but not all of the episodes. Subsequently, in the melon from the first known California case, ASO was found at 2.7 parts per million (ppm). The embargo remained in effect for the next 3 d.

On July 7, all watermelons in retail outlets or in the chains of distribution were destroyed because it was impossible to distinguish ASO-contaminated melons from melons free of ASO. A field certification program was implemented on July 10, and the embargo was lifted. Surveillance after that time identified only one further illness episode in California associated with a melon that tested positive for ASO. Product certification was conducted by the California Department of Food and Agriculture (CDFA) and involved testing composite samples of melons from fields for aldicarb and its metabolites. Melons from fields that tested negative were labeled by CDFA to certify that they had been cleared.

Methods

Commencing late on the morning of July 4, the public was advised through the mass media to report any watermelon-associated illness to their local health department. An active surveillance network set up by CDHS on July 5 involved (a) daily calls to California's 10 regional poison control centers and selected emergency departments, (b) daily contact with all local health departments in California, and (c) periodic calls to several western states and the western provinces of Canada. Local health departments were asked to complete and return an illness report form (described below) to CDHS for all cases reported to them. They were also asked to periodically call selected hospital emergency departments within their jurisdiction so as not to miss illnesses severe enough to require emergency treatment or hospitalization.

The CDHS illness report form and a case-definition algorithm were developed based on the expected cholinergic symptoms resulting from ingestion of aldicarb (Table 1). The case definition divided illness reports into three categories: (1) probable, (2) possible, or (3) unlikely, depending on timing of symptom onset, nature and severity of symptoms, and number of people ill from the same melon.

The CDHS illness report forms were distributed rapidly to local health department officials in an effort to speed collection of uniform case information. The forms included questions about symptoms, time and location of melon purchase, and others who ate the same melon. All reports of illness with date of onset after July 10 were telephoned to CDHS and promptly reviewed by a physician to identify probable poisoning cases from melons bearing certification labels. Additional information was sought from persons who reported illness, if necessary. Samples of melons from probable cases were collected and shipped by local health departments to the nearest participating CDFA or CDHS laboratory for analysis.

Analyses for aldicarb, ASO and aldicarb sulfone (AS) in watermelons were performed by CDFA. In addition, several confirmatory analyses were performed by the U.S. Food and Drug Administration (FDA) regional laboratory in Los Angeles and CDHS's Food and Drug Laboratory. Analyses by CDFA and FDA were performed using liquid chromatography. The minimum detection level was usually 0.2 ppm but ranged between 0.1 and 0.5 ppm ASO. Confirmatory analyses by CDHS were performed using gas chromatography and a method developed by Union Carbide for detecting aldicarb residues in water [method ALDICARB-FPD-WATER(a)].[3] The detection level by this method for all aldicarb residues combined was 0.01 ppm.

Selection of melons for testing was completed in two stages. During the first stage, i.e., prior to July 10, attempts were made to confirm the source and extent of the epidemic. The second stage, after July 10, involved sampling melons from fields that had passed the certification program. The theoretical ability of the field certification sampling plan to detect a single, highly contaminated field was quite good, but given the practical limit of detection of ASO, the necessary compositing of samples, and the large number of fields involved, it was still possible that some contaminated melons might have reached retail markets. Therefore, melons associated with "probable" illnesses that occurred after July 10 were assigned top priority for testing.

Active surveillance continued until the end of August 1985. All case reports were reviewed later for completeness, and additional data were sought when needed. Data from individual case reports were then analyzed using the standardized case definition.

In March 1986, an attempt was made to contact by mail and telephone the 47 women who reported being pregnant when they experienced their watermelon-associated illness. Information was obtained on the pregnancy outcome, birthing complications, birth defects, and any other relevant problems. Six of the 47 were lost to follow-up. Of the remaining 41, 2 denied having been pregnant, and 1 refused to participate. The other 38 women provided information on a standard questionnaire about the outcome of the pregnancy and the baby's health.

Case reports were tabulated in an attempt to identify the geographic source(s) of the epidemic. Illness rates and numbers of illness were mapped by county using SAS/GRAPH, 1980 U.S. Census population denominators, and Tektronix plotter.[4] In an attempt to pinpoint store chains (and through them, wholesalers and farmers) who might have sold contaminated melons, we compared the frequency with which the various chains were identified by "probable" cases and by "unlikely" cases. Our reasoning was that "unlikely" cases probably approximated a random sample of the population as to their use of the various store chains so that we could analyze the data as one would a case-control study. We calculated odds ratios and 95% confidence limits. This measure of association divides the odds of using a particular store chain by "probable" cases by the odds of using that chain among "unlikely" cases. For rare diseases, it is an estimate of the rate ratio, i.e., the incidence of poisoning in patrons of that chain divided by the incidence in nonpatrons. Distributors that served counties or store chains with high odds ratios would be most suspect as sources for contaminated watermelons.

Because of the difficulty in using the complete case definition given in Table 1, which required asking cases about the occurrence of multiple symptoms in several categories, simpler alternative case definitions were explored using data on symptom rates and onset times.

Results

Active surveillance. Case reports were received for dates as early as June 1, 1985. Table 2 shows the number of case reports received in California for the period of active surveillance (June–August 1985) by case classification. In all, 1 376 case reports were received; 78% were classified as probable or possible pesticide poisoning. The geographic distribution of illnesses was evaluated in an attempt to identify the origin of the contaminated melons, but mapping did not suggest a source or sources. Analysis of stores where melons associated with pre-July 10 illness were purchased showed that there were four major supermarket chains involved. Only one of these had a significantly elevated odds ratio, 1.89 (95% confidence limits 1.00 and 3.56), for "probable" vs. "unlikely" illness reports. However, the watermelon distribution systems were too intermingled to quickly determine the suppliers for this chain.

The majority of incidents (61%) involved one person becoming ill after eating a melon. Twenty-two percent of the reports involved 2-person episodes; 10% were 3-person clusters, and 3% were 4-person clusters. Additional clusters involving 5, 6, 9, and 13 persons becoming ill after eating from the same melon also were reported.

Table 1.—Case Definitions for Watermelon-Associated Illness Outbreak—California, July 1985

Classification of Cholinergic Symptoms

Group 1: Gastrointestinal
- Abdominal pain
- Nausea and/or vomiting
- Diarrhea

Group 2: Other peripheral autonomic
- Blurred vision and/or watery eyes
- Pinpoint pupils
- Excess salivation
- Sweating or clamminess

Group 3: Skeletal muscle
- Muscular weakness
- Twitching

Group 4: Central nervous system
- Seizures
- Disorientation or confusion
- Excitation

Classification of Illness Reports

1. **Probable case:**
   Melon positive for aldicarb or aldicarb metabolites; onset ≤ 2 h after consuming melon; AND ONE OF THE FOLLOWING: Multiple groups of cholinergic symptoms or a single group of symptoms and more than one person ill from the same melon; OR onset between 2 and 12 h after consuming melon, multiple symptom groups, and more than one person ill from the same melon.
2. **Possible case:**
   Onset less than 2 h after consuming melon, a single group of symptoms, and no other illnesses reported from the melon; OR onset within 2 to 12 h after consuming melon and multiple symptoms or symptoms from only one group.
3. **Unlikely case:**
   Some other cause of illness judged to be more likely; OR any illness with onset of symptoms more than 12 h after eating melon.

Table 2.—Numbers and Percentages of Watermelon-Associated Illnesses Reported in California, June 1–August 31, 1985, by Onset Date and Case Definition

Case definition	Onset 6/01–7/10		Onset 7/11–8/31		Onset unknown		Total	
Probable	493	(49%)	197	(57%)	2	(8%)	692	(51%)
Possible	269	(27%)	101	(29%)	6	(23%)	376	(27%)
Unlikely	195	(19%)	40	(12%)	0	. . .	235	(17%)
Incomplete	48	(5%)	7	(2%)	18	(69%)	73	(5%)
Total	1 005	. . .	345	. . .	26	. . .	1 376	

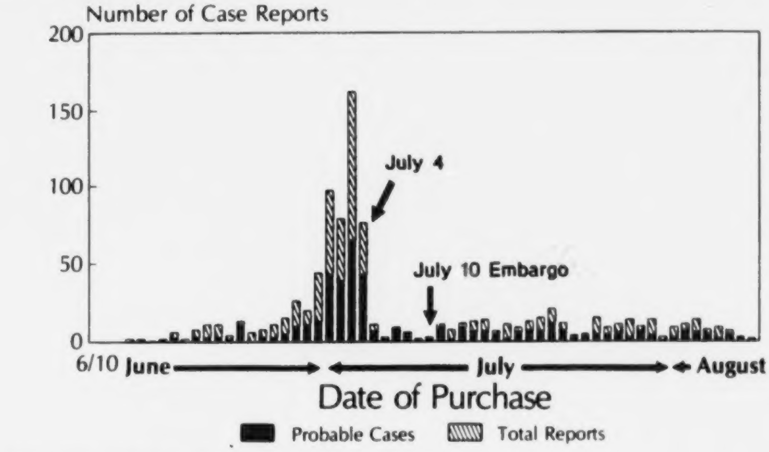
Note: See Table 1 for case definition.

Figure 1 shows the epidemic curve of probable watermelon illness reports within California by date of purchase of melons. The first probable case was reported for a melon purchased June 16; reports rose sharply thereafter. Reports peaked for melons purchased on July 3. There was an abrupt decline in reports for melons purchased after July 4, which coincided with the melon embargo, media advisories, and other measures. Illness onsets for probable cases peaked July 4, and, as with onsets by purchase date, sharply declined after July 4.

Severity of illness. Most people had relatively short-term minor illnesses that resolved quickly; however, some were severely ill. Several reports of cardiac arrhythmias, dehydration, seizures, and other severe illnesses were associated with watermelon consumption before and after July 10 (Table 3). Overall, 17 persons were reported to require hospital admission, 16 of whom were admitted prior to July 10. Of 6 reported deaths, all of which were autopsied, none could be attributed by the coroners to aldicarb/ASO ingestion.

Pregnancy outcomes. Of the 38 women pregnant when they had watermelon-associated illness, 18 were classified as probable cases, 9 as possible, and 10 as unlikely. In one case, the information to classify the illness was inadequate. During the two months immediately after the incident, three pregnancies were investigated. Two near-term pregnancies resulted in stillbirths following acute illnesses associated with watermelon consumption. One pregnant woman had a "probable" illness, and the other had a "possible" illness. Fetal tissues from both stillbirths tested negative for aldicarb and its metabolites (personal communication, Union Carbide Corporation, 1985).

Fig. 1. Watermelon aldicarb illness reports by case definition and melon purchase date California, 1986.



California Department of Health Services

Nine months later an attempt was made to contact the other women who reported being pregnant when they had their watermelon-associated illness. Among the 35 women contacted, 2 neonatal deaths were reported. One was a premature infant born to a mother with "possible" illness, who reported headache and fever 1 wk prior to delivery, raising the possibility that the premature birth and death may have been due to an infection. The second death was due to hypoplastic left heart syndrome; this occurred to a mother with a "probable" illness during the 25th wk of gestation.

Laboratory testing. Of 62 laboratory-tested melons purchased prior to July 10 and associated with illness, 9 (14.5%) were ASO positive. For illnesses associated with melons purchased after July 10, 188 melons were tested, and 1 (0.5%) was ASO positive. In no case was the parent compound aldicarb identified, but some melons contained AS. In addition to the 1 noted aldicarb-positive melon purchased in California after July 10, 2 other aldicarb-positive CDFA-labeled watermelons associated with illness after July 10 were reported in Canada (personal communication, 1985) and Oregon.[1] One of the 3 positive melons found after July 10 could be traced to a particular California field.

Case definition.

The case definition algorithm was compared with symptom reports (Table 4). In general, the 28 with laboratory confirmation of watermelon contamination with ASO were more likely to have had symptoms compatible with carbamate poisoning than those for whom melon tests were negative or not performed. Symptoms reported by at least 50% of those who consumed confirmed ASO-contaminated melons included abdominal pain, nausea, vomiting, diarrhea, blurred vision, salivation, sweating, muscle twitching and/or weakness, and disorientation. These symptoms were also found, but with less frequency, among cases classified as probable, possible, and unlikely. Symptom group 1 (gastrointestinal symptoms) showed the smallest differences in reporting between laboratory-confirmed melon

Table 3.—Severe Illness in California Associated With Watermelon Consumption, Summer 1985.

Condition	Number of cases reported: Before July 10	Number of cases reported: July 10 and after
Seizures	3	0
Loss of consciousness	4	1
Cardiac arrhythmia	6	1
Hypotension	4	0
Dehydration	17	2
Anaphylaxis	3	0

Note: Some individuals had more than one of the above symptoms.

Table 4.—Cases With Various Symptoms, by Case Definition*: California Aldicarb in Watermelon Episode, 1985 †

Symptom	Melon positive‡ for ASO	Illness report classification		
		Probable	Possible	Unlikely
(Total)	28 (100.0)§	689 (100.0)	311 (100.0)	303 (100.0)
Group 1				
Abdominal pain	23 (82.1)	493 (71.6)	212 (68.2)	158 (52.2)
Nausea/vomiting	24 (85.7)	563 (81.7)	250 (80.4)	200 (66.1)
Diarrhea	24 (85.7)	466 (67.6)	179 (57.6)	181 (59.7)
Group 2				
Blurred vision	17 (60.7)	223 (32.4)	31 (10.0)	40 (13.2)
Salivation#	14 (50.0)	128 (18.6)	22 (17.1)	21 (6.9)
Sweating#	20 (71.4)	356 (51.7)	61 (19.6)	59 (19.5)
Group 3				
Muscle//	15 (53.6)	222 (32.2)	41 (13.2)	40 (13.2)
Group 4				
Disorientation	17 (60.7)	208 (30.2)	36 (11.6)	45 (14.9)
Other symptoms				
Breathing**	2 (7.1)	20 (2.9)	4 (1.3)	5 (1.6)
Urination††	5 (17.9)	150 (21.8)	21 (6.8)	22 (7.3)
Fever‡‡	4 (14.3)	151 (21.9)	44 (14.2)	52 (17.2)
Hearing problem	0 (0)	20 (2.9)	9 (2.9)	5 (1.7)

*See Table 1.

†Excludes 45 cases that could not be classified and with untested melons.

‡Not mutually exclusive from other classifications. ASO is a metabolite of aldicarb.

§Values are given as number and percentage, which appear in parentheses.

#Excessive salivation or sweating.

//Muscle weakness and/or twitching.

**Difficulty breathing or shortness of breath.

††Excessive urination or incontinence. Was not included in case definition because of likelihood of urination associated with consumption of a large amount of watermelon.

‡‡As noted by respondent.

cases and the other case groups, and therefore may be the least specific of the cholinesterase inhibitor symptoms. Fever was reported by 14.3% of those who consumed laboratory-positive melons and by 14% to 22% of those in the other groups. Fever was included to differentiate those persons with infectious illness (e.g., viral gastroenteritis), but it failed to do this (possibly because fever was self-reported). To screen for over-reporting, questions were asked about hearing problems; less than 3% of persons in any category reported same.

Several simpler case definitions were developed for illness that occurred within 2 h of watermelon consumption. The following symptom patterns were compared to the more complex case definition used for this outbreak: diarrhea only, nausea and/or vomiting only, diarrhea and nausea/vomiting, and diarrhea or nausea/vomiting. For the four definitions, sensitivity and specificity were calculated. Diarrhea *or* nausea/vomiting within 2 hr of watermelon consumption had the highest sensitivity (79%) and specificity (82%). Hence, if cases with ASO-positive melons had been classified on the basis of these two symptoms alone, 79% of the cases defined as "probable" using the complete definition would have been identified.

Cantaloupe-associated illness. In addition to the reports of watermelon-related illness, there were in this same period 77 illness reports associated with consumption of about 25 cantaloupes. Many of these cantaloupes were tested, and all tested negative for ASO. About half were tested for other pesticide residues (i.e., carbamates, organophosphates, and chlorinated pesticides); none were found. A few complaints about other types of fruit (e.g., honeydew melons) also were received, but none could be linked to any pesticides.

Discussion

Aldicarb is the most acutely toxic pesticide registered in the United States. It has two primary breakdown products: (1) ASO (for rats, LD_{50} = 0.9 mg/kg) and (2) AS (for rats, LD_{50} = 24 mg/kg).[5] With well over 1 000 reports of probable pesticide illness from within and outside California, this episode ranks as the largest recorded North American outbreak of foodborne pesticide illness. In the past, intentional or inadvertent misapplication of aldicarb to cucumbers and mint was associated with similar, though more limited, outbreaks. The spectrum of illness reported in these outbreaks was similar to the current one, ranging from mild to severe. No deaths have been reported from any of these food poisoning episodes.[6-8] In these cases, as with the 1985 watermelon epidemic, identification of the epidemic was dependent on alert clinicians who quickly recognized the symptoms and signs of carbamate pesticide poisoning and on the abilities of laboratories to identify aldicarb metabolites (a test not routinely performed when testing for pesticide residues). Without careful surveillance, it would be easy to overlook such an epidemic because of the nonspecific nature of symptoms of early cholinesterase toxicity.

Aldicarb has been implicated in at least two deaths in agricultural workers.[9,10] Although no deaths in this epidemic were attributable to ASO, the spectrum of clinical illness seen in this episode included many severely ill people. Some of the more serious symptoms and signs reported, such as marked bradycardia and hypotension, could have been lethal, particularly in the very young, the elderly, and the chronically ill. The prompt embargo and widespread publicity almost certainly were responsible for preventing a much larger epidemic and saving lives.

There are no known long-term or reproductive effects of aldicarb and its metabolites in the absence of maternal toxicity, and it is not a suspect carcinogen.[5,11]

One would expect that there would be a certain number of people in the state who had gastrointestinal illness onset coincidentally within 2 h of eating melon; hence, some of the sporadic cases were reported through September. However, underreporting at the beginning of the outbreak may have been substantial, given the long Fourth of July weekend and that the active surveillance system required 1 wk to implement fully. For example, the poison control centers were initially so overwhelmed with calls that they often did not have time to record complete reports; thus, many cases may have been lost to follow-up during the first week of the outbreak. However, a greater proportion of "probable" cases occurred after July 11; this suggests that a reporting bias in favor of minor coincidental illness may have occurred when the epidemic was first reported by the media.

It has been asserted that the entire epidemic was created by media coverage and reporting of illness coincidental with eating aldicarb-contaminated watermelons. However, the episode cannot be explained by coincidence. This is clear from the fact that those with laboratory-positive watermelons were likely to have a greater number of symptoms and more symptoms of severe acetyl cholinesterase inhibition than others.

A study of the geographic case distribution revealed no single retail source for contaminated melons, even when confined to cases confirmed with ASO-Positive tests in melons. This is probably due to the prevailing methods of distributing watermelons, which involve mixing unlabeled melons from numerous different sources. This results in marked intermingling during the distribution process. Any future outbreaks of illness related to watermelon will likely be difficult to trace using epidemiological information alone. This certainly suggests a need for better labeling or tracking methods for watermelons.

There were many illnesses clinically compatible with carbamate poisoning but associated with aldicarb-negative melons. Although, as mentioned above, some of these could have been coincidental occurrences, it is also possible that the laboratory analysis could not detect ASO at levels that can cause illness. This issue has implications for the regulation of pesticide residues in foods and deserves further study.

An outbreak of this explosiveness and magnitude could never have been investigated and documented without the full support and participation of California's local health departments, emergency departments, and poison control centers. The workload generated by this event in these institutions and CDFA is hard to quantify. CDHS has time accounting records that suggest thousands of person hours were devoted by one agency alone. Since the 1985 epidemic, California has begun an integrated food surveillance program that involves local health and environmental health departments, CDFA, and CDHS. Monitoring for pesticide-related illness uses a report form similar to the one used for the 1985 outbreak, but with the simpler case definition for a probable case of carbamate poisoning of diarrhea *or* nausea/vomiting within 2 h of eating produce. This case definition is easier to use in the field and has sufficient sensitivity (79%) so that any future outbreaks of consequence should not be missed, even though it will overlook one of five individual illnesses.

* * * * * * * * * *

Management of this epidemic involved hundreds of individuals in government agencies at all levels and at numerous private institutions. The authors thank all of these persons. Special thanks go to Harvey F. Collins, Ph.D., for his editorial assistance; to Barbara Hopkins, David Epstein, and Martha Harnly, who assisted with data processing and analysis and illustrations; and to Carolyn Harris and Gette Meneses, who typed the manuscript.

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POISONING OF AN URBAN FAMILY DUE TO MISAPPLICATION OF HOUSEHOLD ORGANOPHOSPHATE AND CARBAMATE PESTICIDES

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ABSTRACT

A case report of an urban family who experienced excessive exposure to organophosphate and carbamate pesticides is presented. All three family members developed symptoms that were compatible with cholinesterase inhibition: headache, lightheadedness, wheezing, shortness of breath, nausea, and fatigue. Serial measurement of red blood cell and serum cholinesterases soon after exposure and during subsequent months confirmed the diagnosis of pesticide poisoning. This report demonstrates that the misapplication of pesticides commonly used in residences in urban areas can cause acute pesticide poisoning and demonstrates the usefulness of repeated measurements of cholinesterase during the post-exposure period in establishing the correct diagnosis. *(Key Words: pesticides; organophosphorus compounds; residential facilities; pest control; poisoning, human.)*

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INTRODUCTION

Organophosphate and carbamate pesticides have been well documented to cause acute poisoning in humans in a variety of settings (1,2). These settings include occupational exposures among pesticide applicators, manufacturing workers and farm workers; accidental inhalation, skin absorption and ingestion, especially by children; and intentional attempts at suicide (1-6).

Organophosphates and carbamates are two of the dominant classes of pesticides used for residential pest control in urban areas in the United States. Despite widespread use of these agents and considerable concern about their possible deleterious effects, especially given the large population potentially exposed, there have been few reports of urban residents made acutely or chronically ill by pesticides (5-7).

This report describes a family with clinical and laboratory evidence of acute pesticide poisoning caused by the excessive application of pesticide products used for urban residential pest control.

Environmental History

The affected family consisted of three members, a 32 year-old mother, a 35 year-old father, and their 14 year-old daughter, who were well prior to late November, 1984, when their apartment underwent commercial pesticide application for extermination of fleas. The apartment had been sprayed with unknown pesticides two times several weeks previously without the desired result and without causing illness in the family. The father reported that on November 24, 1984, a professional pesticide applicator sprayed an unknown pesticide using a tank and hose apparatus; he subsequently used eight pressurized canisters (bombs) of a specific pesticide formulation. These canisters were filled with a commercial product containing two active pesticidal ingredients: an organophosphate pesticide, dichlorvos (2,2 dichlorovinyl dimethyl phosphate), and a carbamate pesticide, propoxur (2-(1-methylethoxy) phenol methylcarbamate). Additional "inert" ingredients of the preparation were not identified. Each container was recommended to be used for 6000 cubic feet; the apartment was estimated to have a volume of 7000 cubic feet.

Three hours after application of these pesticides, the father entered the apartment and saw "clouds of vapor still lingering in the air". He covered his face with a cloth, opened the windows of the apartment, and promptly left. He returned with the mother and daughter 3-4 hours later and noted that the previously observed fog of pesticides had cleared; the apartment, however, retained a residual odor of pesticides. The family slept in the apartment that night.

Clinical History

All three family members reported experiencing the following symptoms on the following morning: burning of the throat, chest heaviness, wheezing, shortness of breath, headache, fatigue and nausea. The mother and the daughter also experienced lightheadedness. The mother additionally noted abdominal cramping and loose stools. The father went to work for 8 h, while the others stayed in the apartment. On the following day, the family moved to a local motel for 2 w, during which the apartment was reportedly cleaned twice. Details concerning the extent of cleaning are not available. The family then returned to occupy the apartment, where they noted persistence of the odor of the sprayed material.

All family members visited their personal physician four days after the pesticide application, complaining of the symptoms noted above, which had diminished somewhat during the intervening days. The results of serum and erythrocyte cholinesterase are shown in Table 1. Serum and erythrocyte cholinesterase analyses were performed by Metpath Laboratory (Teterboro, NJ) using kits supplied by Boehringer-Mannheim Diagnostics (erythrocyte cholinesterase) and Gilford (serum cholinesterase) employing a modification of the Ellman method (8).

Upon examination six weeks after initial exposure, the father reported persistence of selected symptoms including headache, fatigue and throat irritation, though these had diminished in intensity. The mother continued to complain of slight shortness of breath, chest tightness, wheezing and minimal abdominal cramping. She reported having used albuterol during the several weeks prior to her visit. The daughter's symptoms had also decreased but she still experienced nausea, headache, sore throat, and some wheezing when in the apartment.

TABLE 1

Recovery of Red Blood Cell Serum and Cholinesterase Levels

		Cholinesterase Levels* Date of Testing			
		11/28/84	1/8/85	2/13/85	Percent Increase**
Father	RBC	3.81	4.30	5.00	24%
	Serum	2.60	7.10	6.00	57%
Mother	RBC	3.20	NA	4.20	24%
	Serum	2.20	5.50	4.20	48%
Daugher	RBC	2.71	3.20	3.80	29%
	Serum	0.90	4.80	3.80	76%

*normal ranges; RBC cholinesterase: 3.00-5.00 IU/mL; serum cholinesterase: 2.50-7.10 units/mL

$$** \ \% \text{ Increase} = \frac{\text{RBC or ChE (2/13/85) - RBC or ChE (11/28/84)}}{\text{RBC or ChE (2/13/85)}} \times 100$$

The father had a history of allergic rhinitis, which occurred only during the spring. He worked as a carpenter. The mother had a past history of childhood asthma, which had abated by the age of 7. She experienced occasional wheezing as an adult, which she treated with a non-prescription bronchodilator. The child also had a history of asthma, which had not been recently active and had received albuterol from her personal physician during the current illness.

Physical examinations of all three family members were normal with the exception of minimal wheezing on forced expiration heard in the lower left lung of the mother. Pulmonary function tests performed on the two adults were also normal, except for a minimal decrease in the mother's forced vital capacity (78% predicted).

Sequential measurements of serum and red blood cholinesterase over the three month period following the incident until mid-February 1985 are provided in Table 1. The father's initial values of serum and erythrocyte cholinesterase were within normal limits (2.60 μ/mL and 3.81 IU/mL, respectively). The mother's serum cholinesterase level was initially low, 2.20 U/mL, and her erythrocyte cholinesterase was normal at 3.20 IU/mL. The daughter had low initial values of both serum and erythrocyte cholinesterase levels (0.90 U/mL and 2.71 IU/mL, respectively). All measurements were performed by Metpath.

Repeat testing of red blood cell and serum cholinesterase on all three patients in January and February, 1985, showed significant increases in values for these tests during the intervening 6 and 11 weeks. All members of the family demonstrated a 24 to 29% increase in the erythrocyte cholinesterase from the immediate post-exposure measurement to the measurement obtained 11 weeks later. The mean increase was 26.1% (paired t = -19.92, two tail p = .003) (9). For the serum cholinesterase, there was a 48 to 76% increase for all members in the family during the same time interval. The mean increase was 59.4% (paired t = -6.75, two tail p = .021) (9).

DISCUSSION

Diagnosis of mild to moderate organophosphate or carbamate poisoning is frequently difficult (1,10). The symptoms are non-specific and mimic other common disorders, such as viral infections. Laboratory confirmation of the diagnosis of such poisoning is, therefore, essential in all but the most severe clinical cases or in circumstances of obvious over-exposure to relevant pesticides. The clinical significance of any specific level of erythrocyte or plasma cholinesterase is measured by its percent decrease from a baseline pre-exposure level or by the degree to which the values are frankly below the established reference range (11).

Laboratory assessment of organophosphate or carbamate poisoning is complicated, however, by the relatively high inter-individual and intra-individual variability in levels of erythrocyte and serum cholinesterase. The coefficient of variation in cholinesterase between individuals is relatively high, ranging from 13% to 16% or higher for erythrocyte cholinesterase (1,12,13) and 15% to 27% for plasma cholinesterase (1,12,14).

Intra-individual variation over time is somewhat lower. The average coefficient of intra-individual variation for plasma and erythrocyte cholinesterases in the published literature ranges from 7.6% to 11.3% (1, 15-17), though individual samples may fluctuate as much as 25% (1,17,18).

According to Gallo and Lawryk (1), if one pre-exposure cholinesterase measurement is available, then the subsequent depression of cholinesterase must be at least 20% for the plasma enzyme and 15% for the erythrocyte enzyme to reflect a significant statistical change. The percentage alterations in erythrocyte cholinesterase of 24-29% and of serum cholinesterase of 48% to 75% are higher than that expected due to normal variation.

While having pre-exposure measurements of cholinesterase levels in individuals is preferred due to the narrower intra-individual variation, they are usually not available in cases with non-occupational exposure to pesticides (11,19). In the absence of such pre-exposure measurements, sequential post-exposure measurements can be used to estimate the pre-exposure cholinesterase levels in the patients. Midtling and others described an outbreak of acute mevinphos poisoning among a group of 16 lettuce growers in California who developed symptoms compatible with organophosphate poisoning. Cholinesterase levels rose in the weeks following the outbreak of illness (4). In this report, the father had normal values initially for both erythrocyte and serum cholinesterases. Sequential measurements taken 6 and 11 weeks later, however, clearly demonstrated that the father experienced the recovery of cholinesterase levels of the same magnitude as the other two family members.

Of note is that the serum cholinesterase was more severely inhibited in these cases than the erythrocyte cholinesterase, an effect that has been previously observed with dichlorvos (20). It is possible that the recovery of the erythrocyte cholinesterase may be underestimated in this report since the interval between the first and last cholinesterase measurements was less than 12 weeks, which is the average life span of erythrocytes and the period over which a diminished level of erythrocyte cholinesterase can be expected to normalize. Serum cholinesterase, on the other hand, recovers in one to three weeks.

Many of the symptoms experienced by the exposed persons in the present report - chest tightness, shortness of breath, headaches, lightheadedness, fatigue, nausea, and diarrhea - are compatible with the diagnosis of mild to moderate organophosphate and carbamate poisoning. Many of these same symptoms may be caused by excessive exposure to the solvent carriers that are often contained in commercial pesticide formulations. In the absence of exposure measurements or the identity of the solvents that were likely present, solvents may have contributed to the symptoms experienced. However, the level of cholinesterase inhibition strongly supports the contention that anti-cholinesterase activity was a significant factor in the complex of symptoms suffered by this family.

The persistence of symptoms, albeit attenuated, after six weeks following initial exposure is not fully explained. Since the levels of the cholinesterases had reverted to the normal range by six weeks, the symptoms that were still present at six weeks were not due to the short-term anti-cholinesterase effect of dichlorvos and propoxur. One possible explanation is that exposure to other toxins such as the solvent carriers continued, which is unlikely in view of the repeated cleaning of the apartment and the expectedly rapid volatilization of the solvents typically used as carriers. Another possible explanation is the lingering of the symptoms associated with cholinesterase inhibition, even in the absence of active inhibition. There is limited evidence of the persistence of symptoms beyond the immediate period of organophosphate poisoning (4,21), though most of the studies of persistent effects have focused on central nervous system effects rather the multi-organ symptoms that characterize acute organophosphate poisoning (22-24).

Use of pesticides in buildings and on lawns is widespread throughout the United States and represents an important means by which a large proportion of the population of the United States is potentially exposed to pesticides. Instances of organophosphate or carbamate poisoning such as described in this case report are unusual in the medical literature (5-7). This may be due to the widespread safe use of pesticides, the difficulty in diagnosing mild acute and chronic pesticide poisoning, or the general lack of knowledge on the part of health care providers about eliciting environmental and occupational information from patients (25). With the progressive interest in environmental health, it is likely that additional cases of environmental pesticide poisoning will be recognized, especially if a carefully elicited environmental and occupational history results in the appropriate clinical and laboratory assessment of potential cases of such poisoning.

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ATSDR
June 1990
Case Studies in Environmental Medicine

13

Polynuclear Aromatic Hydrocarbon (PAH) Toxicity

Environmental ALERT . . .

- ☑ *Due to combustion of fossil fuels and organic waste, PAHs are ubiquitous in the environment.*
- ☑ *Certain PAH metabolites are believed to interact with DNA, causing malignancies and heritable genetic damage.*
- ☑ *In humans, PAHs are associated with cancers of the lung and skin, and possibly with urologic, gastrointestinal, laryngeal, and pharyngeal cancers.*

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. The Agency for Toxic Substances and Disease Registry (ATSDR) and the Centers for Disease Control (CDC) designate this continuing medical education activity for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association and 0.1 continuing education units for other health professionals. See pages 17 to 19 for further information.

Guest Contributor: Jacek Brudzewski, MD
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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

Dyspnea, weight loss, and weakness in a 52-year-old incinerator worker

A 52-year-old man is seen at your office for a health evaluation, his first in 3 years. While trying to assure you that he is in reasonably good health, he admits that this visit was prompted by his wife, who is concerned about his weight loss, lack of stamina, and weakness in the shoulders and arms. Chart review indicates a weight loss of 30 pounds since his last visit. The patient also describes shortness of breath with moderate activity. He is a lifelong nonsmoker and drinks alcohol only occasionally. He is taking no medications. Past history is noncontributory. Review of systems reveals the patient also has a chronic, intermittently productive cough and constipation of 1 month's duration.

Social history indicates that the patient has worked at a municipal incineration plant for the past 34 years and has been a lifelong resident of an urban industrial neighborhood approximately 1 mile from where he works. He has been married for 25 years; his wife and adult daughter are in good health.

On physical examination, vital signs are normal. Inspection of the skin reveals multiple dry, scaly, hyperpigmented macules involving the forehead, temporoparietal areas, eyelids and brows, and several hyperkeratotic papillomata about the face, neck, upper chest, forearms, and hands. On palpation of the right supraclavicular area, a 2 x 3-cm firm, nontender fixed lymph node is detected. Auscultation discloses intermittent, scattered right-sided wheezes and dry bibasilar crackles. The remainder of the exam is unremarkable.

Laboratory results are remarkable for the following: hemoglobin 12.9 g/dL (normal 14 to 18 g/dL), hematocrit 36% (normal 42 to 52%), leukocyte count 2.9 x $10^3/\mu L$ (normal 3.9 to 11 x $10^3/\mu L$), serum calcium 12.9 mg/dL (normal 8.5 to 10.5 mg/dL), alkaline phosphatase 483 IU/L (normal 30 to 125 IU/L) with concomitant elevation of GGTP (GGT), SGOT (AST) 121 IU/L (normal 7 to 45), and SGPT (ALT) 129IU/L (normal 7 to 35 IU/L). The chest X ray reveals a 3.3-cm central, thick-walled, cavitating lesion with irregular, spicular margins in the right upper lobe, and atelectasis and prominence of the right hilar lymphatics.

Pretest

(a) *What should be included on this patient's problem list?*

(b) *What is the differential diagnosis?*

(c) *What treatment would you recommend for this patient?*

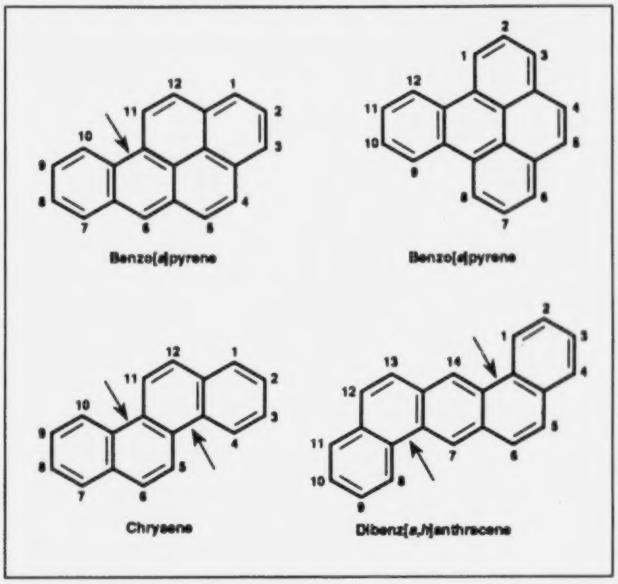
Answers to the Pretest can be found in Challenge answers (5) through (7) on page 15.

Exposure Pathways

- **PAHs are a class of organic compounds produced by incomplete combustion or high-pressure processes.**
- **PAHs are ubiquitous in the environment.**

Polycyclic aromatic hydrocarbons (PAHs) are organic compounds consisting of three or more fused benzene rings containing only carbon and hydrogen (Figure 1). PAHs form when complex organic substances are exposed to high temperatures or pressures. Hundreds of such compounds exist. They are a natural component of most fossil fuels.

Figure 1. Structural formulas of selected polyaromatic hydrocarbons (PAHs). The arrows indicate "bay" regions (discussed on page 6).



At room temperature, PAHs are solids with low volatility. They are soluble in many organic solvents and are relatively insoluble in water. Most PAHs can be photo-oxidized and degraded to simpler substances.

PAHs are ubiquitous in the environment. Also known as polynuclear aromatics (PNAs) or polycyclic organic matter (POM), the more common PAHs include benzo(a)pyrene, benzo(e)pyrene, benzo(a)anthracene, chrysene, pyrene, benzo(k)fluoranthene, benzo(g,h,i)perylene, coronene, dibenz(a,h)anthracene, and dibenz(a,h)acridine. Benzo(a)pyrene (B[a]P) is the most carcinogenic PAH studied.

☐ **Cigarette smoke contains numerous PAHs.**

Although PAHs are produced naturally by forest fires and volcanoes, most PAHs in ambient air are the result of burning coal, wood, petroleum, petroleum products, or oil; and of coke production, refuse burning, and motor vehicle exhaust. PAHs are found in industries that produce or use coal tar, coke, or bitumen (asphalt); they are also produced in coal gasification plants, smokehouses, municipal incinerators, and some aluminum production facilities. In cities with coke ovens the concentration of airborne PAHs may reach 150 nanograms per cubic meter of air (ng/m^3). (The permissible workplace exposure limit for coke oven emissions is 150,000 ng/m^3.) Coal tar pitch and creosote, which are complex mixtures of liquid and solid aromatic hydrocarbons produced in coke ovens, contain significant amounts of B(a)P and other PAHs.

Water and soil contain measurable amounts of PAHs, primarily from airborne fallout. Water contamination also occurs from industrial effluents and accidental spills during oil shipment at sea. Documented levels of PAHs in soil near oil refineries have been as high as 200 nanograms per kilogram (ng/kg) of dried soil; those from soil samples obtained near cities and areas with heavy traffic typically are greater by tenfold. PAHs can leach from soil into water. Concentrations of B(a)P in drinking water are generally lower than those in untreated water and about a hundredfold lower than the U.S. Environmental Protection Agency's (EPA) proposed drinking water standard. (EPA's proposed maximum contaminant level goal [MCLG] for B(a)P in drinking water is 0.2 parts per billion [ppb].)

PAH concentrations in foodstuffs vary. Charring meat or barbecuing food over a charcoal fire greatly increases the concentration of PAHs. Cooked and smoked meats and fish are higher in PAHs than uncooked products, with up to 2.0 micrograms per kilogram (µg/kg) of B(a)P detected in smoked fish. Roasted peanuts and coffee, refined vegetable oil, and many other foodstuffs contain PAHs, and some crops such as wheat, rye, and lentils may synthesize PAHs.

Cigarette smoke contains numerous PAHs. According to one study, a cigarette yields 10 to 50 ng B(a)P, 18 ng chrysene, 40 ng dibenz(a,h)anthracene, and 12 to 140 ng benz(a)anthracene. Filtered cigarettes remove some, but not all, PAHs from cigarette smoke inhaled by the smoker.

Challenge

(1) What are likely sources of PAHs for the patient described in the case study?

Who's at Risk

- ☐ **Persons working with coal and coal products have a greater likelihood of exposure to PAHs.**
- ☐ **AHH-inducible persons may be at greater risk from PAHs' effects.**

Percival Pott, an English surgeon, was the first to report a connection between occupation and cancer. In 1775, he described an unusually high incidence of scrotal cancer among London chimney sweeps and suggested this was due to their exposure to soot and ash. Since then other coal tar-related cancers have been induced in laboratory animals and noted in humans. The PAH benzo(a)pyrene, which was isolated from coal tar in the 1930s, was determined to be carcinogenic when applied to the skin of test animals. Since then, hundreds of PAHs have been described; many of them are carcinogenic.

Workers in industries or trades using or producing coal or coal products are at highest risk of PAH exposure and include, but are not limited to, the following:

- aluminum workers
- asphalt workers
- carbon black workers
- chimney sweeps
- coal-gas workers
- coke oven workers
- fishermen (coal tar on nets)
- graphite electrode workers
- machinists
- mechanics, auto and diesel engine
- printers
- road (pavement workers)
- roofers
- steel foundry workers
- tire and rubber manufacturing workers
- workers exposed to creosote:
  - carpenters
  - farmers
  - railroad workers
  - tunnel construction workers
  - utility workers

Fetuses may be at risk of PAHs' effects. Various animal studies have confirmed that PAHs and metabolites cross the placenta, affecting the offspring. Animals exposed to PAHs *in utero* show a decrease in the number of functional oocytes, often to the point of infertility. Because PAHs are excreted in breast milk, nursing infants of exposed mothers can be secondarily exposed.

Persons with a high degree of aryl hydrocarbon hydroxylase (AHH) inducibility may constitute a high-risk population. Genetic variation in AHH inducibility has been implicated as a determining factor for susceptibility to lung and laryngeal cancer. Several studies support the hypothesis that persons with lung cancer have higher AHH inducibility in cultured lymphocytes or in peripheral lung tissue than those who do not develop lung cancer.

Challenge

(2) Besides the patient, who in the case study may be at risk of PAH exposure?

Biologic Fate

PAHs are absorbed through ingestion, inhalation, and dermal contact. Although no precise data regarding the metabolic fate of PAHs exists for humans, information on absorption, distribution, and elimination of these substances is available from animal studies. After absorption, PAHs enter the lymph, circulate in the blood, are metabolized primarily in the liver and kidney, and are excreted in both bile and urine. Because of their lipophilic nature, PAHs can accumulate in breast milk and adipose tissue; however, biliary and urinary excretion of PAHs is relatively efficient because of the wide distribution of enzymes that transform PAHs into polar metabolites.

☐ **PAHs are metabolized in a number of organs and are excreted in bile and urine.**

☐ **PAHs are excreted in breast milk and are stored to a limited degree in adipose tissue.**

In addition to the liver and kidneys, metabolism of PAHs occurs in adrenal glands, testes, thyroid, lungs, skin, sebaceous glands, and small intestine. PAHs are probably transformed initially to epoxides, which are converted to dihydrodiol derivatives and phenols. Glucuronide and sulfate conjugates of these metabolites are excreted in the bile; glutathione conjugates are further metabolized to mercapturic acids in the kidney and are excreted in the urine. Metabolism is a prerequisite for hepatobiliary excretion and elimination through the feces, regardless of route of entry.

Some parent PAHs are weak carcinogens and require metabolism to become more potent carcinogens. Diol epoxides, proposed PAH intermediate metabolites, are presumed to be mutagenic and may affect normal cell replication when they react with DNA to form adducts. The bay region theory states that an epoxide will be highly reactive if it is located in the "bay" region of the PAH molecule (Figure 1).

Challenge

(3) Additional information for the case study: the patient's daughter, who has lived in his household all her life, recently gave birth to a daughter. Is the newborn at risk from PAH exposure?

Physiologic Effects

☐ **The most significant endpoint of PAH toxicity is cancer.**

PAHs generally have a low degree of acute toxicity to humans. Many PAHs are only sightly mutagenic or even nonmutagenic *in vitro*; however, their metabolites or derivatives can be potent mutagens. Interaction of PAH metabolites with DNA is believed to be the mechanism of PAH-related carcinogenesis.

The carcinogenicity of certain PAHs is well established in laboratory animals; increased incidence of skin, lung, liver, and stomach cancer have been reported, as well as injection-site sarcomas. Animal studies indicate that certain PAHs also can affect the hematopoietic and immune systems, and can produce reproductive and developmental effects.

Carcinogenicity

Epidemiologic reports of PAH-exposed workers have noted increased incidences of skin, lung, bladder, and gastrointestinal cancers. These reports, however, provide only qualitative evidence of the carcinogenic potential of PAHs in humans due to the presence of multiple PAH compounds and other putative carcinogens and indicate the lack of quantitative monitoring data.

☐ **Increased incidences of lung, skin, GI, and genitourinary cancers are associated with occupational exposure to PAHs.**

The earliest human PAH-related epidemiologic study was reported in 1936 by investigators in Japan and England who studied lung cancer mortality among workers in coal carbonization and gasification processes. Subsequent U.S. studies among coke oven workers confirmed an excess of lung cancer mortality with the suggestion of excessive genitourinary system cancer mortality. Later experimental studies showed PAHs in soot were probably responsible for the increased incidence of scrotal cancer among London chimney sweeps noted by Percival Pott.

PAH-induced carcinogenesis may result when a PAH-DNA adduct forms at a site critical to the regulation of cell differentiation or growth. A mutation occurs during cell replication if the aberration remains unrepaired. Cells affected most significantly by acute PAH exposure appear to be those with rapid replicative turnover, such as those in bone marrow, skin, and lung tissue. Tissues with slower turnover rates, such as liver tissue, are less susceptible.

Challenge

(4) How could you document that the work environment of the patient described in the case study contributed to his risk of lung cancer?

Clinical Evaluation

History and Physical Examination

☐ **Physical examination includes review of all systems.**

Pertinent history includes the patient's occupational history, occupation of spouse and other household members, medications including coal tar-containing dermatologic preparations, and diet, especially charbroiled meats, alcohol consumption, and smoking habits. Hobbies and activities may reveal additional evidence of exposure to PAH-containing mixtures.

Physical examination should include review of all systems, keeping in mind that cancer is the most significant endpoint of chronic PAH toxicity. If PAH exposure is suspected, the clinician should be alert to malignant transformation of actinic skin lesions. The bucal mucosa and oropharynx should be inspected for malignant changes. Inspection of sun-exposed areas for evidence of hyperpigmentation in response to sunlight is advised. Patients who chronically inhale PAHs should have periodic chest X rays and pulmonary function tests.

Signs and Symptoms

Acute Exposure

☐ **Acute effects attributed to PAH exposure are probably caused by other agents.**

PAHs have low acute toxicity. Other, more toxic agents probably cause those acute symptoms attributed to PAHs. Hydrogen sulfide in roofing tars and sulfur dioxide in foundries are examples of concomitant, acutely toxic contaminants.

Chronic Exposure

☐ **Effects reported from occupational exposure to PAHs include chronic bronchitis, dermatitis, cutaneous photosensitization, and pilosebaceous reactions.**

The following is a list of reported effects associated with chronic exposure to coal tar and its byproducts:

Skin: erythema, burns, warts on sun-exposed areas with progression to cancer. Toxic effects of coal tar are enhanced by exposure to ultraviolet light.

Eyes: irritation and photosensitivity.

Respiratory system: cough, bronchitis, and bronchogenic cancer.

Gastrointestinal system: leukoplakia, bucal-pharyngeal cancer, and cancer of the lip.

Hematopoietic system: leukemia (inconclusive) and lymphoma.

Genitourinary: hematuria, kidney and bladder cancers.

Laboratory Tests

Direct Biologic Indicators

Although researchers have examined PAHs directly in the blood and tissues of experimental animals, these methods have not been widely used for human samples. High costs of testing and lack of knowledge of normal background levels in humans limit their clinical usefulness.

☐ **Direct biologic measurement of PAHs is neither cost-effective nor clinically useful.**

Indirect Biologic Indicators

The most common tests for determining exposure to PAHs involve examining tissues, blood, and urine for the presence of metabolites. For example, tissue in culture can be labeled with radioactive phosphorus and analyzed by thin-layer chromatography and scintillation to identify and quantify the DNA adducts formed. Also, an immunoassay technique, for which a patent is pending, has been developed to detect antibodies to the PAH-DNA adducts in blood.

☐ **A recently developed technique measures serum antibodies to PAH-DNA adducts.**

Recently it has been established that PAH diol epoxides form adducts with hemoglobin in the red blood cells; the adducts can be quantified using fluorescence spectroscopy. This technique is limited in its potential usefulness, however, due to individual differences in PAH metabolism and the limited specificity of the technique itself.

In general, biologic monitoring can be useful in determining whether exposure to PAHs has occurred, but it is not clinically useful for evaluating individual patients because normal or toxic levels have not been determined. Individual variability, confounding effects of drugs or cigarettes, and nonspecificity of techniques are likely to complicate the interpretation of the results, especially in low-level environmental exposures.

Challenge

(5) Before his present employment, the patient was employed as a laborer on a farm. He denies exposure to pulmonary toxic agents such as asbestos or silica. What is the problem list and differential diagnosis for the patient described in the case study?

(6) What is the significance of elevated levels of aryl hydrocarbon hydroxylase?

Treatment and Management

Acute Exposure

- ☐ **Decontamination and life-support measures are the primary objectives after acute PAH exposure.**

Contaminated clothing should be removed from victims as soon as possible. The skin should be decontaminated by gently scrubbing with soap and water. Ocular contamination should be treated with irrigation and a complete eye examination. In the event of an acute inhalation exposure, ventilatory support should be tailored to the patient's clinical condition. Most acute respiratory injury in PAH-containing work environments occurs from exposure to gases, fumes, and dusts containing various toxic agents rather than to PAHs.

Chronic Exposure

- ☐ **Treatment of chronic PAH toxicity is symptomatic.**
- ☐ **Education is an important aspect of patient care.**

Treatment of PAH-related disease begins with patient education. Persons exposed to potentially significant levels of PAHs should be aware of the increased risk of cancer and the additive effect of cigarette smoke and other toxic agents. Periodic evaluation of healthy patients who have been significantly exposed to PAHs, even in the absence of symptoms, is recommended to facilitate early diagnosis and intervention should a malignancy develop.

Predicting the carcinogenicity of a complex chemical mixture on the basis of one or several of its components is difficult because of possible interactions among the components. Interactions of various PAHs have been shown to produce both synergistic and antagonistic effects in mutagenicity tests *in vitro*. Because estimation of additional risk due to PAH exposure is often impossible, the challenge to the clinician is maintaining a balance between appropriate concern and undue alarm.

Challenge

(7) The diagnosis for the patient described in the case study is lung cancer with classification T2, N3, M0. What treatment do you recommend?

(8) In general, what can you do to decrease the risk of lung cancer among your patients?

Standards and Regulations

Workplace

Air

☐ **The OSHA PEL for PAHs in the workplace is 0.2 mg/m³.**

The PAH workroom air standard mandated by the Occupational Safety and Health Administration (OSHA) is an 8-hour time-weighted average (TWA) permissible exposure limit (PEL) of 0.2 mg/m³, measured as the benzene-soluble fraction of coal tar pitch volatiles. The OSHA standard for coke oven emissions is 0.15 mg/m³. The National Institute for Occupational Safety and Health (NIOSH) has recommended that the workplace exposure limit for PAHs be set at the lowest detectable concentration, which was 0.1 µg/m³ at the time of the recommendation. The standards and regulations for PAHs are summarized in Table 1.

Table 1. Standards and regulations for PAHs

Agency	Focus	Level	Comments
ACGIH	Air - Workplace	0.2 mg/m³	Advisory; TWA[†]
NIOSH	Air - Workplace	0.1 mg/m³	Advisory; Recommended exposure limit
OSHA	Air - Workplace	0.2 mg/m³	Regulation; (Benzene soluble fraction of coal tar volatiles) PEL[§] over 8-hour workday
EPA	Water	0.2 ppb	Proposed maximum contaminant level goal (MCLG) for B(a)P; Proposed MCLG for PAHs is zero

[*] ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration

[†] TWA (Time-Weighted Average) = time-weighted average concentration for a normal 8-hour workday and 40-hour workweek to which nearly all workers may be repeatedly exposed.

[§] PEL (Permissible Exposure Limit) = highest level in air, averaged over a normal workday, to which a worker may be exposed.

Environment

Water

In 1980, EPA developed ambient water quality criteria to protect human health from the carcinogenic effects of PAH exposure. The recommendation was a zero (nondetectable) level for carcinogenic PAHs in ambient water. Because attainment of this level may be currently impossible, EPA will recommend maximum contaminant level goals (MCLG) for individual PAHs in June 1990. The MCLG for B(a)P, the most carcinogenic PAH, will be 0.2 ppb. EPA is also considering setting MCLGs for five additional carcinogenic PAHs: benz(a)anthracene, benzo(k)fluoranthene, chrysene, dibenz(a,h)anthracene, and indenopyrene.

☐ **The maximum contaminant level goal for B(a)P in drinking water is 0.2 ppb.**

Food

No standards for governing the PAH content of foodstuffs have been established by the Food and Drug Administration.

Challenge

(9) Would you consider the patient described in the case study a sentinel case requiring notification of public health agencies? Explain.

Suggested Reading List

Reviews

Zedeck MS. Polycyclic aromatic hydrocarbons: a review. J Environ Pathol Toxicol 1980; 3:537-67.

Biologic Testing

Harris CC, Newman MJ, Weston A, Mann DL. Identification of human antibodies to polycyclic aromatic hydrocarbon-DNA adducts. Clin Res 1986;34:690A.

Haugen A, Becher G, Benestad C et al. Determination of polycyclic aromatic hydrocarbons in the urine, benzo(a)pyrene diol epoxide-DNA adducts in lymphocyte DNA, and antibodies to the adducts in sera from coke oven workers exposed to measured amounts of polycyclic aromatic hydrocarbons in the work atmosphere. Cancer Res 1986;46:4178-83.

Jongeneelen FJ, Bos RP, Anzion RBM, Theuws JL, Henderson PT. Biological monitoring of polycyclic aromatic hydrocarbons: metabolites in urine. Scand J Work Environ Health 1986;12:137-43.

Metabolism and Carcinogenesis

Levin W, Wood A, Chang RL, et al. Oxidative metabolism of polycyclic aromatic hydrocarbons to ultimate carcinogens. Drug Metab Rev 1982;13:555-80.

Related Government Documents

Agency for Toxic Substances and Disease Registry. Toxicological profile for polycyclic aromatic hydrocarbons (draft). Atlanta: US Department of Health and Human Services, Public Health Service, 1990.

Agency for Toxic Substances and Disease Registry. Toxicological profile for benzo(a)pyrene. Atlanta: US Department of Health and Human Services, Public Health Service, 1988.

Agency for Toxic Substances and Disease Registry. Toxicological profile for dibenz(a,h)anthracene. Atlanta: US Department of Health and Human Services, Public Health Service, 1988.

Agency for Toxic Substances and Disease Registry. Toxicological profile for benz(a) anthracene. Atlanta: US Department of Health and Human Services, Public Health Service, 1988.

Agency for Toxic Substances and Disease Registry. Toxicological profile for benzo(b)fluoranthene. Atlanta: US Department of Health and Human Services, Public Health Service, 1988.

Environmental Protection Agency. Health effects assessment for polycyclic aromatic hydrocarbons (PAH). Cincinnati: Environmental Criteria and Assessment Office, 1984. EPA report no. 540/1-86-013.

Environmental Protection Agency. An exposure and risk assessment for benzo(a)pyrene and other polycyclic aromatic hydrocarbons. Vol IV. Washington DC: Office of Water Quality. Report no. EPA 4-85-020-V4.

Answers to Pretest and Challenge Questions

(1) The patient may have been exposed to incinerator-generated pollutants at his work for over 34 years. Moreover, if his home and immediate environs are in the prevailing downwind direction from the incinerator plant, there may be ambient air contamination from ash, dust, soot, and smoke. The patient may have been exposed to PAHs by all three routes: inhalation, ingestion, and direct cutaneous contact.

(2) Workers at the incinerator plant and residents in the community downwind from the incinerator may be exposed to PAHs. The patient's family members may have added exposure if the patient carried these compounds home on his skin and work clothes.

(3) Yes, if the patient's daughter breathed contaminated air in and around the house, engaged in various household chores such as laundering, dusting, and general cleaning of the contaminated home or her father's work clothing, then the baby could have been exposed in utero. PAHs absorbed into the mother's system may continue to be transferred to the infant via breast milk. The newborn may also be breathing contaminated air, thereby increasing her exposure.

(4) The role of the workplace in the patient's PAH exposure can be determined by area sampling at the work site, individual monitoring, medical surveillance of coworkers, and air sampling within the immediate community. A first step would be to determine if this data is available through sources at the incinerator plant and local, state, or federal agencies. While this information most likely will not aid the diagnosis or influence the treatment or outcome of a specific case, it may have legal and financial implications in workers' compensation issues.

(5) The patient's problem list includes weight loss, fatigue, muscle weakness, skin lesions on exposed areas, exertional dyspnea, and a roentgenographically identified cavitating lesion in the right upper lobe with associated lymphadenopathy. The differential diagnosis includes carcinoma of the lung, tuberculosis, fungal lung infection, and lung abscess.

(6) Aryl hydrocarbon hydroxylase (AHH) inducibility is genetically determined. An elevation in pulmonary and serum levels of this enzyme signifies an additional risk factor for the development of pulmonary and laryngeal carcinoma. The test, however, is a research tool and is not readily available.

(7) The patient has squamous cell carcinoma and his condition is considered inoperable. Treatment options would consist of radiation or radiation with chemotherapy.

(8) The main objective is to educate patients about cancer prevention. You should try to stimulate changes in their work habits and lifestyle that will decrease the risk of developing cancer. A risk assessment can identify elements in a person's workplace, family history, medical history, and lifestyle that may be controllable risk factors.

For example, between 75% and 80% of all cases of bronchogenic carcinoma are due to cigarette smoking and are therefore preventable. Of the remaining 20% to 25%, many are occupationally or environmentally related and could therefore be prevented by appropriate workplace or environmental controls. Education for smoking prevention, improved working conditions, substitution of less hazardous materials in work processes and building materials, and increased awareness of personal risk factors may decrease the incidence of lung cancer.

(9) Squamous cell carcinoma does not require a report to any public health agency or authority. However, in view of the patient's medical, social, occupational, and family history, workplace and environmental factors emerge as the most likely causal factors in the development of his neoplastic disease. When the potential exists for others to be exposed, serious illness related to occupational or environmental factors should be reported to the appropriate state and federal authorities. For example, OSHA would have responsibility for PAHs in the workplace air at the incinerator site, and EPA would have responsibility for the level of emissions to the ambient air or water. Inclusion of this case in a tumor registry should also be considered.

Sources of Information

More information on the adverse effects of PAHs and the treatment and management of PAH-exposed persons can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Polyaromatic Hydrocarbons (PAHs) Toxicity* is one of a series. For other publications in this series, please use the order form on the back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of Director, at (404) 639-0730.

ATSDR June 1990

Case Studies in Environmental Medicine

12

Polychlorinated Biphenyl (PCB) Toxicity

Environmental ALERT . . .

☑ ***PCBs have caused elevated liver enzyme levels and chloracne in humans, and may have reproductive effects.***

☑ ***PCBs cause cancer in animals and may be carcinogenic in humans.***

☑ ***PCBs are environmentally persistent and concentrate upward in the food chain.***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. The Agency for Toxic Substances and Disease Registry (ATSDR) and the Centers for Disease Control (CDC) designate this continuing medical education activity for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association and 0.1 continuing education units for other health professionals. See pages 17 to 19 for further information.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

A 48-year-old handyman with progressive cystic acne and abnormal liver function

You have been treating a 48-year-old man conservatively for his facial acne vulgaris. He first sought treatment about 3 months ago, remarking that such blemishes are typical for a teenager but he never had them during adolescence. Therapy was initiated with benzoyl peroxide washes and topical antibiotics, in addition to instructions for skin hygiene. When no real improvement was noted, oral antibiotics were prescribed. Due to continued lack of efficacy, this regimen was later supplemented by Retin-A™* (tretinoin) cream.

The patient has returned for a follow-up visit and complains that the acne is worse. On examination, you agree, and tell the patient you would like to refer him to a dermatologist for Accutane™* (isotretinoin) therapy. A serum biochemical and hematologic profile are ordered to document baseline values before therapy begins.

To your surprise, the biochemical panel reveals the following abnormalities: total bilirubin 2.8 mg/dL (normal 0-1.5), direct bilirubin 0.4 mg/dL (normal 0-0.4), SGPT (ALT) 74 IU/L (normal 0-50), SGOT (AST) 88 IU/L (normal 0-50), GGPT (GGT) 190 IU/L (normal 15-85), LDH 230 IU/L (normal 50-225). Other testing, including complete blood count, alkaline phosphatase, BUN, creatinine, and urinalysis are within normal limits.

On questioning, the patient denies history of hepatitis, contact with hepatitis patients, other liver difficulties or blood transfusion. He informs you he has Gilbert's syndrome and has had elevated bilirubin levels in the past. There is no family history of cardiovascular disease or cancer. The patient does not smoke; he drinks 2 to 3 bottles of beer each evening, and sometimes more on weekends. He is currently taking no medications other than those mentioned. Review of systems is otherwise unremarkable.

Social history reveals the patient is married with three teenaged children; his wife and children are in good health. They live in a high-rise apartment building where the patient has been handyman and part-time building manager for the last year. He spends much time in the basement area, which includes a workshop, recreation room with pool table, and laundry and heating facilities. An avid fisherman, he spends most weekends fishing in Lake Michigan with his two sons. Physical examination reveals mild, nontender hepatomegaly without jaundice. His acne, which is most prominent on the upper face lateral to the eyebrows, began about 8 months ago.

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* Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

Pretest

(a) What should be included in the patient's problem list?

(b) What is a differential diagnosis for the patient's altered liver enzymes?

(c) What tests would be useful in helping you arrive at a diagnosis?

Answers to the Pretest can be found on page 15.

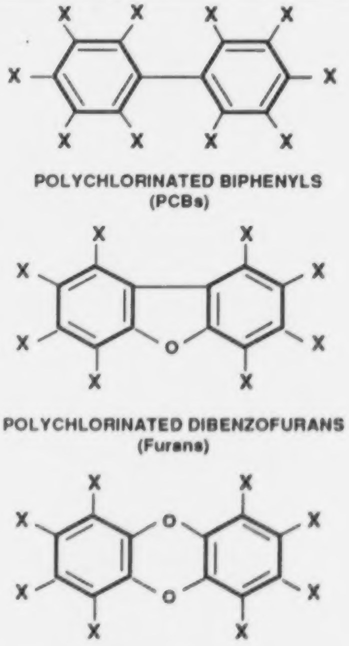
ATSDR

Exposure Pathways

- ☐ **PCBs persist in the environment, concentrating upward in the food chain.**
- ☐ **The primary nonoccupational source of PCB exposure is food, especially fish from contaminated water.**

Polychlorinated biphenyls (PCBs) are a family of 209 chemicals with varying numbers of chlorine atoms attached in varying positions to two connected benzene rings (Figure 1). Commercial PCB products are always mixtures of PCBs and are usually contaminated with small amounts of polychlorinated dibenzofurans (furans) or polychlorinated dibenzodioxins (dioxins). Contamination by furans is a concern because their toxicity is generally much greater than that of PCBs.

Figure 1. Polychlorinated biphenyls and related compounds


POLYCHLORINATED BIPHENYLS (PCBs)
POLYCHLORINATED DIBENZOFURANS (Furans)
POLYCHLORINATED DIBENZODIOXINS (Dioxins)
X
O

X = Chlorine or Hydrogen

Because of their insulating and nonflammable properties, PCBs have been used as heat exchange and dielectric fluids in transformers and capacitors, hydraulic and lubricating fluids, diffusion pump oils, plasticizers, extenders for pesticides, and as ingredients of caulking compounds, paints, adhesives, and flame retardants. PCBs have also been used in inks and carbonless paper. Trade names for PCBs include Aroclor, Askarel, Eucarel, Pyranol, Dykanol, Clorphen, Asbestol, Diaclor, Nepolin, and EEC-18.*

PCB mixtures are colorless to dark brown oils, viscous liquids, or sticky resinous semi-solids. They evaporate slowly at room temperature; however, their volatility increases dramatically with small increases in temperature. Overheated equipment that contains PCBs can vaporize significant quantities of these compounds, causing an inhalation hazard, especially in areas where ventilation is poor.

Today PCBs are found mainly in transformers and capacitors manufactured before the U.S. Environmental Protection Agency (EPA) banned the production of PCBs in 1977. Many of these old transformers and capacitors are still contained in industrial equipment (such as welding equipment), medical equipment (such as X-ray machines), and household appliances (such as refrigerators). Ballasts of fluorescent light fixtures may contain PCBs. During normal lighting operation, the PCBs are entirely enclosed; however, when the capacitor wears out, it may burn or break and leak PCBs.

PCBs can be released into the general environment from poorly maintained toxic waste sites; by illegal or improper dumping of PCB wastes, such as transformer fluids; through leaks or fugitive emissions from electrical transformers containing PCBs; and by disposal of PCB-containing consumer products in municipal landfills. PCBs have been found in at least 271 of 1177 hazardous waste sites on the EPA National Priorities List. Of the 1.25 billion pounds of PCBs produced in this country since 1929, about 450 million pounds have found their way into the environment. The chemical stability of these synthetic compounds accounts for their persistence in the environment. Another important reason for their persistence is their resistance to biodegradation.

Low levels of PCBs can be found throughout the world. PCBs in water or on soil surfaces evaporate and return to earth by rainfall or settling of dust particles. Because PCBs strongly adsorb to soil particles, significant leaching from soil and translocation to plants do not occur. Although PCBs are widespread in the aquatic environment, their low water solubility helps to prevent high concentrations in drinking water supplies.

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* Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

Food can be a major source of PCB exposure, usually from fish and animal fat. PCBs are lipophilic; they preferentially separate from water and adsorb to sediment. Bottom feeders and other aquatic organisms then ingest and accumulate PCBs, resulting in bioconcentration upward in the food chain. Composite analysis of commercial whole fish collected from Lake Ontario in 1980 found PCB levels of 0.11 to 4.90 parts per million (ppm).

The toxicity of PCBs was dramatically illustrated in 1968 when over 1600 people in Japan were poisoned by cooking oil contaminated with PCBs from a heat transfer unit. The contaminating oil likely contained furans and dioxins, compounds generally more toxic than PCBs themselves. The ensuing illnesses became known as "Yusho" (rice oil disease).

Challenge

(1) Additional information for the case study: In response to your persistent, detailed questioning regarding his hobbies and possible contact with hepatotoxins, the patient reveals that while in the basement workshop he frequently wipes up a "dark, oily discharge" near a large electrical transformer in the work area. The discharge has also resulted in a gummy residue on tools and other surfaces. He mentions he sometimes feels dizzy and nauseated after working in the basement all day.

Is there an association between the clinical findings and this additional information?

Who's at Risk

Although PCBs are no longer manufactured in the United States, the greatest potential for exposure to PCBs still occurs in the workplace. For example, workers may inhale or have dermal contact with PCBs during repair or maintenance of process equipment or electrical transformers and during accidents or spills involving PCBs. Exposure can also occur in disposal of PCB-containing materials at hazardous waste sites. Occupations entailing risk of PCB exposure include, but are not limited to, the following:

electric cable repair
electroplating
emergency response
firefighting
hazardous waste hauling/site operating
heat exchange equipment repair
maintenance cleaning
metal finishing
paving and roofing
pipefitting/plumbing
timber products manufacturing
transformer/capacitor repair
waste oil processing

Nonoccupational exposures have also occurred. The public has encountered PCBs through illegal roadside dumping of hazardous waste oils and through inhalation of smoke and soot from transformer or capacitor fires. Pyrolysis of PCBs can produce dioxins and furans, placing smoke-inhalation victims at increased risk of exposure to these toxic compounds.

Fetuses and neonates are potentially more sensitive to PCBs than adults because of transplacental distribution and physiologic differences. They lack the hepatic microsomal enzyme systems that facilitate metabolism and excretion of PCBs. Furthermore, PCBs accumulate in breast milk. Nursing infants are at additional risk because human milk contains a steroid that inhibits PCB glucuronidation and excretion.

Other populations potentially more sensitive to PCBs are persons with compromised hepatic functioning, including those with incompletely developed glucuronide conjugation mechanisms due to congenital disorders such as Gilbert's syndrome, and persons with hepatic infections. Persons taking medications potentially toxic to the liver may also be at increased risk.

☐ **Certain workers can be exposed to PCBs during repair of equipment and accidents or spills.**

☐ **Fetuses and neonates may be more sensitive to PCBs than adults; nursing infants are at increased risk of exposure from PCB-exposed mothers.**

☐ **Persons with compromised hepatic function may metabolize PCBs less efficiently than healthy persons.**

Challenge

(2) Are other sources of PCB exposure likely for the patient described in the case study?

Biologic Fate

- ☐ **PCBs are stored in lipid tissues.**
- ☐ **The liver is the primary site of PCB metabolism.**
- ☐ **The slow metabolism of PCBs leads to bioaccumulation.**

PCBs are readily absorbed into the body but slowly metabolized and excreted. After absorption, PCBs partition between the aqueous and lipid compartments of the body in a biphasic pattern. During the first day after PCBs were administered to laboratory animals, they were distributed mainly to the liver and muscle tissue. In a second phase, PCBs were redistributed to the adipose tissue, skin and other fat-containing organs. More highly chlorinated PCBs redistribute to adipose tissue to a greater extent than do PCBs with a lower percentage of chlorine; the presence of more highly chlorinated PCBs appears to delay excretion of the lesser chlorinated compounds for reasons not clearly understood.

The liver is the primary site of PCB metabolism by hydroxylation and conjugation with glucuronic acid and sulfates. The rate of metabolism depends on the number and position of chlorine atoms, with lesser chlorinated isomers being more readily metabolized.

Excretion of PCBs is slow, so bioaccumulation occurs even at low exposure levels. As long as exposure continues, a true steady state is never achieved. PCBs metabolized with more difficulty are excreted almost exclusively by the biliary route; metabolites of PCBs with a smaller percentage of chlorination are eliminated through bile and urine. Urinary metabolites are in the form of conjugates, including glucuronides and sulfates.

There are essentially no pharmacokinetic data for humans. PCB half-lives in the rat range from 1 day to 460 days depending on the degree of chlorination.

Background levels in human sera are typically less than 20 parts per billion (ppb), and residues measured in human milk have ranged from 40 to 100 ppb. Reported levels in adipose tissue range from 1 to 2 ppm.

Challenge

(3) Explain why patients with Gilbert's syndrome may be at increased risk of adverse effects due to PCB exposure.

Physiologic Effects

In humans, PCB toxicity affects the skin and liver, and may have developmental effects. Metabolic, reproductive, endocrine, and immunosuppressive effects have been noted in animals, but have not been adequately studied in humans. Although data from animal studies indicate that PCBs are definitely animal carcinogens, data from PCB-exposed human populations are inconsistent and inconclusive.

☐ **PCBs have low potential to cause acute effects.**

☐ **EPA considers PCBs to be probable human carcinogens.**

Dermatologic Effects

Chloracne is the only overt effect of PCB exposure in humans, but absence of chloracne does not rule out exposure. There is no reliable dose-response model for chloracne in exposed populations; the dose-response relationship may be dependent upon individual predisposition. Chloracne typically develops weeks or months after exposure. The lesions are often refractory to treatment and can last for years. One case persisted for more than 30 years.

☐ **PCB-induced chloracne can reflect systemic toxicity.**

The acneform lesions arise from altered differentiation of acinar sebaceous base cells into keratinocytes. The chin, periorbital, and malar areas are affected most often, although lesions may also appear on the chest, arms, thighs, genitalia, and buttocks–areas not commonly affected by acne vulgaris. The most distinctive lesions are cystic and measure from 1 to 10 millimeters (mm). Other prominent lesions are comedo. The cysts and comedones can become inflamed and secondarily infected. The papules and cysts may be surrounded by edema and erythema. Chloracne may result not only from dermal contact but also from ingestion and generally indicates systemic toxicity.

Besides chloracne, Yusho patients had hyperpigmentation of the skin, conjunctiva, gingiva, and nails. These pigmentation disturbances have also been noted in some PCB-exposed workers.

Hepatic Effects

☐ **High-level PCB exposure may produce elevated levels of liver enzymes.**

☐ **Evidence suggests that PCBs cause hepatotoxicity in humans.**

Epidemiologic studies and clinical surveys indicate that severe occupational exposure to PCBs can increase serum liver enzymes. The enzyme levels often show inconsistent patterns, however, and increases generally have not been associated with hepatic dysfunction, although approximately 10% of the Yusho patients experienced jaundice. Asymptomatic hepatomegaly has been reported in workers, many of whom had concomitant elevated serum PCB levels. Some researchers believe that aspartate aminotransferase (SGOT or AST) and gamma glutamyl transpeptidase (GGTP or GGT) are the most sensitive indicators of PCB exposure in humans, and that changes in these liver enzymes may occur at exposure levels below those at which chloracne appears. Liver damage, histologically documented, is the most consistent finding among laboratory animals tested with PCBs.

Increases in urinary porphyrin levels have been noted in a study of workers with low-level PCB exposure. Changes in porphyrin metabolism may be triggered by the induction of liver microsomal enzymes. PCBs are more potent enzyme inducers than phenobarbital, a drug that occasionally causes clinical problems due to its enzyme-inducing effects, and PCBs' enzyme-inducing effects can persist long after cessation of exposure. The health implications for enzyme induction include the occurrence of disease secondary to increased metabolism of endogenous or exogenous substances, and interference in medical therapy due to increased metabolism of administered drugs.

Reproductive and Developmental Effects

The Yusho incident documents PCBs' potential to cause developmental and fetotoxic effects in humans. Two of the Yusho mothers had stillbirths; 10 of 13 infants had abnormal skin pigmentation, 9 of 13 had ocular discharge, and 12 of 13 were smaller than average. Two infants developed Yusho from breast feeding. In contrast, the authors of a study of nursing infants whose mothers were occupationally exposed to PCBs found no adverse health effects. Contaminants in the PCB oil cannot be ruled out as factors in Yusho disease. Follow-up of the Yusho infants revealed no persistent morphologic or behavioral abnormalities.

☐ **PCBs have a potential to cause developmental and fetotoxic effects in humans.**

In laboratory animals, changes in estrous cycles, failure of ovum implantation, increased frequency of spontaneous abortions, and low birth weight of offspring have been reported after PCB exposure. No teratogenic effects have been reported in studies of humans or animals.

Carcinogenicity

The epidemiologic evidence is insufficient to evaluate the potential of PCBs as human carcinogens. Although Yusho victims showed a slightly higher rate of deaths from neoplasms 15 years after the incident, the data were not adjusted for age or smoking and drinking patterns. Cancer data from other human populations are inconsistent and inconclusive.

☐ **PCBs are considered potential human carcinogens on the basis of results from animal studies.**

Data from animal studies have shown that PCBs cause hepatocarcinomas, pituitary tumors, leukemia, lymphomas, and gastrointestinal tract tumors. On the basis of these data, EPA considers PCBs to be probable human carcinogens.

Challenge

(4) Is there a need to be concerned about PCB exposure when the clinical effects of the patient in the case study seem so limited?

Clinical Evaluation

History and Physical Examination

A detailed history will facilitate the diagnosis of chronic PCB poisoning. Pertinent information includes occupational histories of all household members, medications, and diet, including ethanol intake. During the physical examination, physicians should pay particular attention to the skin and hepatic system. Encountering a patient with PCB toxicity should trigger consideration of whether this is a sentinel event, indicating the possibility of other similarly exposed persons such as coworkers or family members.

Signs and Symptoms

Acute Exposure

☐ **Chloracne is the only known overt sign of PCB toxicity; however, absence of chloracne does not rule out exposure.**

PCBs have very low potential for producing acute toxic effects. The only overt sign of PCB exposure is chloracne, which is described on page 7. Acneform lesions do not appear in all severely exposed patients (only 82% of Yusho patients had chloracne); therefore, its absence does not rule out exposure. New cases of chloracne should be reported to the local or state health department.

Elevated liver enzymes are the most sensitive effect of PCB exposure in animals and have been detected in several human epidemiologic studies. Hepatomegaly has also been noted in some PCB-exposed workers.

Chronic Exposure

☐ **Because of an EPA ban on PCB production in 1977, chronic exposure in the workplace is uncommon today.**

Many people chronically exposed to PCBs have had no overt signs or symptoms of toxicity. In others, reported signs and symptoms of exposure with hepatic involvement have included weight loss, anorexia, nausea, vomiting, jaundice, and abdominal pain. The degree of liver injury was related to the degree of chlorination in the PCBs, dose and duration of exposure, and possible concurrent exposure to other hepatotoxins, infectious agents, or certain medications. Headache, dizziness, and edema have also been reported. Chronic PCB exposure in the workplace is unlikely to occur today.

Laboratory Tests

Direct Biologic Indicators

Some researchers believe that PCB blood levels after long-term exposure correlate well with adipose tissue levels. However, PCB analysis of either blood or adipose tissue is expensive and time-consuming and is not recommended unless exposure has been massive. Breast milk analysis for PCBs should not be considered unless the exposure is severe. PCBs detected in breast milk are not necessarily an indication that breast-feeding should be stopped.

- ☐ **Serum or adipose tissue PCB levels may indicate exposure, but they are difficult to interpret clinically.**

Indirect Biologic Indicators

Liver function tests may be the most sensitive sign of PCB toxicity in the absence of chloracne; however, these measures are of questionable value because they are nonspecific. Also, normal liver enzyme values do not rule out significant exposure; body burden still may be elevated. PCB conjugates can often be detected in urine after exposure. Their analysis is expensive, unreliable, and not recommended.

- ☐ **Elevated liver-enzyme levels are of limited value in diagnosing PCB exposure.**

Challenge

(5) What confirmatory laboratory test can be ordered to establish the diagnosis of PCB exposure?

(6) Additional information for the case study: The patient requasts a serum PCB analysis. The laboratory reports a level of 125 ppb, with no normal range indicated. How will you interpret this report?

Treatment and Management

Acute Exposure

☐ **There is no antidote for PCB exposure; treatment is symptomatic.**

In the event of PCB splashes in the eyes, irrigate with tepid water immediately for at least 15 minutes, and follow with ophthalmic evaluation. Remove contaminated clothing and discard properly. Gently wash affected skin with soap and warm water for at least 15 minutes.

In the rare event that PCB-containing substances are ingested, induce vomiting immediately if the patient is conscious. Gastric lavage may be subsequently administered at a medical facility until the gastric washings are clear. Activated charcoal has not been proven beneficial, but is not contraindicated. Exposed persons should have periodic follow-up examinations with particular attention to hepatic function and dermal lesions.

Chronic Exposure

☐ **Removal from the source is the goal of treatment for PCB exposure.**

There is no specific treatment for PCB toxicity. Diagnostic workup should be limited to liver function tests and dermatologic examination, with skin biopsy of lesions. Initial treatment of chloracne is based on cessation of exposure, good skin hygiene, and use of dermatologic measures commonly employed for acne vulgaris. If these measures are not efficacious, the patient should be referred to a dermatologist.

The carcinogenic potential of PCBs should be carefully reviewed with the patient, primarily to allay anxiety. Since there are no known methods of reducing reserves of PCBs in lipid tissues, attempts to purge the body of PCBs should not be undertaken. Saunas and nutritional therapies have no proven efficacy. Crash diets risk mobilizing PCBs stored in fat.

Since PCBs are hepatotoxins, history of exposure to other potentially hepatotoxic agents should be obtained and patients should be encouraged to avoid exposure to other hepatotoxins such as antibiotics or medications with known hepatotoxicity, alcohol, and chlorinated solvents.

Challenge

(7) What steps should be recommended to patients when PCB-related health effects are suspected?

Standards and Regulations

Workplace

Air

The Occupational Safety and Health Administration's (OSHA) permissible exposure limit (PEL) is a time-weighted average (TWA) airborne concentration of 1000 μg/m³ for PCBs containing 42% chlorine (average molecular formula of $C_{12}H_7Cl_3$). PCBs with 54% chlorine and an average molecular formula of $C_{12}H_5Cl_5$ have a PEL of 500 μg/m³. Both standards encompass all physical forms: aerosols, vapor, mist, sprays, and PCB-laden dust particles. OSHA considers that PCBs are absorbed through intact skin; therefore, dermal as well as inhalation exposure routes, should be evaluated by an industrial hygienist.

☐ **OSHA's PEL is 1000 μg/m³ for PCBs containing no more than 42% chlorine, and 500 μg/m³ for compounds containing up to 54% chlorine.**

The National Institute for Occupational Safety and Health (NIOSH) recommends a ten-hour TWA of 1 μg/m³ based on the minimum reliable detectable concentration and potential carcinogenicity of PCBs. NIOSH also recommends that all workplace exposures be reduced to the lowest feasible level.

Environment

Water

EPA considers PCBs a probable human carcinogen and prohibits industrial discharges under the Clean Water Act Effluent Guidelines. Currently, there is no legal maximum contaminant level for PCBs in drinking water. However, EPA advises that the

☐ **EPA does not have a standard for PCBs in drinking water.**

level of PCBs in drinking water be limited to 0.5 ug/L on the basis of carcinogenicity at 10^{-4} to 10^{-6} risk levels.

Food

The Food and Drug Administration (FDA) mandates tolerances of 0.2 to 3.0 ppm PCBs for all foods, with a tolerance level in fish of 2 ppm. FDA also limits PCBs in plastic food-packaging materials to 10 ppm.

Challenge

(8) What regulatory steps should be taken for the situation described in the case study?

Suggested Reading List

Clinical

Kimbrough RD. Human health effects of polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs). Annu Rev Pharmacol Toxicol 1987;27:87.

Letz G. The toxicology of PCBs–an overview for clinicians. West J Med 1983;138:534-40.

McKenna JP, Moskovitz M, Cox JL. Abnormal liver function tests in asymptomatic patients. Am Fam Physician 1989;39(3):117-26.

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Acquavella JF, Hanis NM, Nicolich MJ, Phillips SC. Assessment of clinical, metabolic, dietary, and occupational correlations with serum polychlorinated biphenyl levels among employees at an electrical capacitor manufacturing plant. J Occup Med 1986;28(11):1177-80.

Fischbein A, Wolff MS, Bernstein J, Selikoff IJ. Dermatological findings in capacitor manufacturing workers exposed to dielectric fluids containing polychlorinated biphenyls (PCBs). Arch Environ Health 1982;37(2):69-74.

Weaver G. PCB contamination in and around New Bedford, Mass. Environmental Science Technology 1983;18:22A-7A.

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Fischbein L. Toxicology of chlorinated biphenyls. Annu Rev Pharmacol 1974. 14: 139-56.

IARC (International Agency for Research on Cancer). IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Lyon, France: World Health Organization, 1982.

Related Government Documents

Agency for Toxic Substances and Disease Registry. Toxicological profile for selected PCBs. Atlanta: US Department of Health and Human Services, Public Health Service, 1989. NTIS report no. PB/89/225403/AS.

Environmental Protection Agency. Drinking water criteria document for polychlorinated biphenyls (PCBs). Washington, DC: US Environmental Protection Agency, 1988. EPA report no. ECAO-CIN-414.

Answers to Questions

Pretest

The pretest can be found on page 1.

(a) The patient's problem list includes acne vulgaris, which is atypical because of the location of the lesions and their late onset without history of outbreaks during adolescence. The mildly altered liver functions are nonspecific in their interpretation and clinically unexpected. Gilbert's syndrome is a hereditary, relatively common, benign, unconjugated hyperbilirubinemia. It may contribute to the laboratory findings of elevated bilirubin (especially after a fast) but would not explain the clinical picture or elevated liver enzymes.

(b) The combination of asymptomatic hepatomegaly and mild nonspecific elevations of hepatic enzymes in this case is suggestive of a chronic inflammatory liver process or hepatitis. The causes of hepatitis can be classified as drug-induced, toxic, infectious, genetic, and connective tissue disease-associated. The major cause of liver disease in the United States is alcohol ingestion. Less common are environmental exposures, resulting in either acute or chronic toxic hepatitis. Infectious hepatitides include those due to the viruses such as A (infectious), B (serum), C (transfusion-associated) and other possible agents of non-A, non-B hepatitis. Some connective tissue diseases such as lupus erythematosus are associated with a specific type of hepatitis. Hepatitis may also occur with Epstein-Barr virus and cytomegalovirus infections.

Infiltrative diseases such as sarcoidosis or amyloidosis, and rare genetic diseases such as Wilson's disease, primary hemochromatosis, and alpha$_1$-antitrypsin deficiency must be excluded.

(c) Viral serology and a heterophil antibody test should be considered. If there are suggestive signs or symptoms, a serum iron and total iron binding capacity, serum copper and ceruloplasmin, and antinuclear antibodies may be helpful. Assays for suspected hepatotoxins may also be of value. Further evaluation may include ultrasound and percutaneous liver biopsy.

Challenge

Challenge questions begin on page 4.

(1) Older electrical transformers and capacitors can contain PCBs as a dielectric and heat transfer fluid. Leaks in the equipment could allow PCBs to volatilize under conditions of increased temperature, such as those in a basement. A person with chronic exposure to the residue could eventually receive a significant PCB dose through both dermal and inhalation routes.

(2) Great Lakes fish, particularly from Lake Michigan, are known to be a potential source of PCBs. A correlation between consumption of PCB-contaminated fish and elevated serum PCB levels has been shown in a study of residents of New Bedford, Massachusetts. For the general population, however, a clinically significant human body burden of PCBs is unlikely to occur through fish consumption alone.

(3) Persons with Gilbert's syndrome have decreased UDP-glucuronyltransferase activity, resulting in impaired glucuronidation of bilirubin and, presumably, of PCBs also. Since a PCB elimination pathway is excretion of the glucuronide in urine, impaired capacity to conjugate PCBs with glucuronic acid can theoretically lead to accumulated PCBs and greater body burden. This hypothesis has never been tested, however.

(4) Yes, it is important to be aware that potential carcinogenicity is the main reason PCB production was banned in the United States. Human evidence is still considered inadequate, but the animal evidence was strong enough for EPA, NIOSH, and IARC (the International Agency for Research on Cancer) to conclude that PCBs may have carcinogenic effects in humans.

(5) Selected laboratories have the capability to perform PCB analyses on human tissue. The lipophilic nature of PCBs causes them to accumulate in fat; consequently, analysis of adipose tissue obtained by biopsy has been advocated as a measure of long-term exposure. Serum PCB analysis, which is less invasive than fat biopsy, can also be done. However, such tests are expensive and health risks often cannot be determined from the results. Testing human tissue for PCB content, therefore, remains principally a research tool.

(6) A correlation between increasing levels of serum PCBs and dermatologic findings, including chloracne, has not been consistently found in human epidemiologic studies. However, one study involving 153 workers with occupational exposure to PCBs showed 22 subjects with dermal abnormalities and a mean plasma PCB level of 87 ppb, while 131 subjects without abnormalities had a mean serum level of 50 ppb. The difference was statistically significant. By comparison, plasma PCB levels in unexposed populations are less than 30 ppb. However, no serum PCB values are yet accepted as normal or toxic levels. Our patient's PCB serum level of 125 ppb is nonetheless consistent with PCB exposure as an etiology for his unusual acne, and PCB exposure may be contributing to the hepatic effects noted.

(7) The first response is clearly to stop the exposure. In this case, the patient should stay away from the basement until the transformer is repaired and the basement area cleaned. He should also refrain from eating Great Lakes fish until his PCB level normalizes and the fish are known to be uncontaminated. Avoiding exposure is especially important, as there is no specific treatment for PCB accumulation. The need to avoid other hepatotoxic substances including alcohol should be stressed. Currently, there are no data to support monitoring serum PCB levels.

(8) Since cessation of exposure is of prime importance, the physician can be most helpful by specifically recommending proper abatement. In this case, the owner of the building should be notified of the potential health hazard. This may require the assistance of local, state, or federal agencies such as the department of public health and EPA. These agencies can work cooperatively with those involved to bring about remediation of the harmful exposure. It is important to prevent others from using the basement areas until cleanup is complete.

ATSDR **October 1993**

Case Studies in Environmental Medicine

34

Ionizing Radiation

Environmental ALERT . . .

☑ ***Everyone is exposed to ionizing radiation. Approximately 82% of this exposure is natural background from cosmic and terrestrial sources, and 18% is due to man-made sources.***

☑ ***Public exposure to ionizing radiation or contamination of the environment by radioactivity engenders intense fear. The emotional and psychologic stresses resulting from exposure should be recognized and addressed early in a radiation incident.***

☑ ***Health care providers should understand the physics, chemistry, and biology of radiation to communicate effectively about it.***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. See page 35 for more information about continuing medical education credits and continuing education units.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

Radiation contamination caused by a transportation accident

You are a physician on duty in the emergency department of a hospital in a community of approximately 40,000 residents. At 7:45 A.M. you receive notification of a vehicular accident about 4 miles northeast of the city. A truck carrying radioactive material struck a guard rail and rolled 200 feet down an embankment. The truck, which came to rest at a point about 15 feet from the river bank, is on fire. The driver of the truck has minor burns on his hands and a deep laceration of the scalp; he is conscious but somewhat confused and incoherent. His assistant, a passenger in the truck, has second-degree burns on his hands and a simple fracture of his lower left leg.

A member of the highway patrol, who was first on scene and noticed the radioactivity placard on the truck, contacted a health physicist from the regional office of the Department of Energy. The health physicist found that the driver of the truck and his assistant are externally contaminated with the radioactive material, which is emitting beta and gamma radiation. The health physicist also detected radioactive contamination along the truck's path as it rolled down the embankment. Three ruptured containers of radioactive material were found near the truck; it is believed that their contents may have entered the river. The community you serve relies on the river for drinking water, as well as for recreational activities.

State police have rerouted traffic and placed road blocks at all points within a 3-mile radius of the accident. However, a young boy whose family is vacationing on a houseboat about 20 yards from the site where the truck came to rest, is known to have approached the scene immediately after the accident occurred. The highway patrol is attempting to locate the boy.

Pretest

(a) *Where could you obtain consultation on treatment and management of persons contaminated with radioactivity?*

(b) *Describe appropriate initial management of the driver and his assistant.*

(c) *Is the young boy who has not been located in danger? Explain.*
Are the other occupants of the houseboat at risk as a result of the accident?

(d) *If the radioactive material entered the river and consisted of aqueous potassium iodide, what steps could be taken to protect the residents of your community who rely on the river for drinking water? Would these steps differ if the radioactive waste consisted of cesium-137 in solution?*

Answers to the Pretest can be found on pages 31-32.

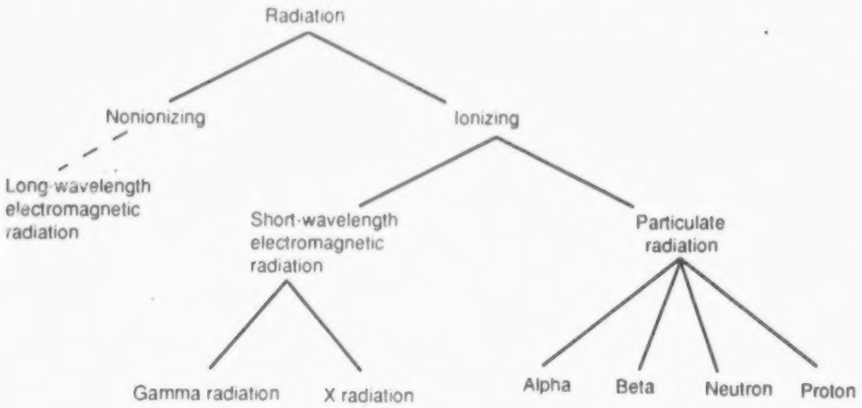
Introduction

- ☐ **Radiation is of two types: ionizing and nonionizing.**
- ☐ **The nature of ionizing radiation is particulate (e.g., alpha or beta radiation) or wave-like (e.g., X or gamma radiation).**

The nuclear reactor accidents at Three Mile Island in Pennsylvania in 1979 and at Chernobyl in the USSR in 1986 have increased the public's concern about exposure to radiation. Awareness of the potential health effects of elevated levels of radon in homes has intensified that concern. The purpose of this document is to help clinicians answer patients' questions about the early and long-term effects of radiation exposure, the risks of radiation in diagnostic and therapeutic medical procedures, and the potential dangers of radiation to the fetus and future generations.

Events just before the turn of the century, which included Roentgen's discovery of X rays and Becquerel's recognition of natural radioactivity, allowed us to understand how radiation is produced and how it interacts with matter. Radiation may be of two types, ionizing or nonionizing (Figure 1). Ionizing radiation is capable of physically disrupting neutral atoms by dislodging orbital electrons, thus forming an ion pair consisting of the dislodged electron and the residual atom. Ion pairs are chemically reactive and may produce toxic agents in the cell (e.g., free radicals from water), which can interfere with normal life processes. Nonionizing radiation, on the other hand, does not dislodge orbital electrons or destroy the physical integrity of an impacted atom. The health effects of nonionizing radiation are not addressed in this document.

Figure 1. Types of Radiation



Adapted from: Leach-Marshall JM. Analysis of radiation detected from exposed process elements from the krypton-85 fine leak testing system, page 50. Semiconductor Safety Association Journal 1991; 5(2): 48-60.

Ionizing radiation exists as either particles or electromagnetic waves. Particulate radiation (e.g., alpha particles, beta particles, neutrons, and protons) has finite mass and may or may not carry a charge. Electromagnetic radiation, on the other hand, has no mass or charge; it consists of electric and magnetic forces that move at the speed of light in consistent patterns of various wavelengths. The continuum of wavelengths constitutes the electromagnetic spectrum. The shorter wavelengths—gamma radiation and X radiation—have high energies, and like particulate radiation, are capable of ionizing matter. The longer wavelengths of the electromagnetic spectrum, which include radio waves; microwaves; and infrared, visible, and ultraviolet radiation have relatively low energies and are nonionizing.

Not all forms of ionizing radiation have the same biologic effects. Generally speaking, for directly ionizing particles, the ion density along the path of low-energy radiation is greater than that along the path of high-energy radiation; low-energy radiation moves slower and has more time to interact. However, the total pathway of low-energy radiation is usually shorter, so the total number of interactions may well be less than with high-energy radiation. Similarly, the ion density toward the end of the radiation path is greater than at the beginning because the velocity of the radiation is less and the probability of interaction is greater. Alpha particles are capable of producing the highest specific ionization (i.e., greatest number of ion pairs per unit length of path), followed in order by beta particles and electrons. X radiation and gamma radiation interact with matter by transferring energy to electrons. (For more information, see *Appendix I, Forms of Ionizing Radiation*.)

The units that have evolved to measure ionizing radiation are the result of its many facets. Radiation units (Table 1) may characterize the (1) energy, (2) radioactive decay rate, (3) effect in air, (4) ability to be absorbed by matter, or (5) biologic effect. Units may be modified by prefixes such as *milli* (indicating thousandths of the base unit), *micro* (millionths), *pico* (billionths), *kilo* (a thousand times), or *mega* (a million times).

The units used most commonly in this document are rad (radiation absorbed dose) and rem (roentgen equivalent in man or mammal). The rad describes the dose of radiation in terms of the amount of energy absorbed by a given mass, for example, of water or tissue. The absorption of 100 ergs of ionization energy in 1 gram of water has a value of 1 rad.

Use of the rem takes into account the biologic effectiveness of the various types of radiation. The rem is numerically equal to the rad multiplied by a Radiation Weighting Factor (formerly "quality factor"). The Radiation Weighting Factor (RWF) reflects differences in the amount of each type of radiation necessary to produce the same biologic effect. For beta, gamma, and X radiation, RWF is 1.0, making their effect on tissue equivalent. The RWF for alpha particles is 20, indicating its biologic effect is 20 times greater than the effect of beta, gamma, or X radiation.

Table 1. Units of radiation measurement

Characteristic	Unit	Description
Energy	electron volt (eV) (also ergs, joule)	Kinetic energy of an electron as it moves through a potential difference of 1 volt.
Rate of radioactive decay	curie (Ci)*	Radioactivity emitted per unit of time (1 Ci = 3.7 x 10^{10} disintegrations per second).
Air exposure	roentgen (R)	Amount of X and gamma radiation that causes ionization in air. One roentgen of exposure will produce about 2 billion ion pairs per cubic centimeter of air.
Absorbed dose	rad	Dose resulting from one roentgen of ionizing radiation deposited in any medium, typically water or tissue. One rad results in the absorption of 100 ergs of ionizing radiation per gram of medium.
Biologic effectiveness	rem	Dose of any form of ionizing radiation that produces the same biological effect as 1 roentgen; 1 rem = 1 rad x Radiation Weighting Factor (RWF), where the value of RWF depends on the type of radiation as follows: X radiation = 1.0 gamma radiation = 1.0 beta =1.0 alpha = 20 neutrons = 5 to 20, depending on their energy

A new System Internationale (SI) nomenclature has been adopted, which is used by international, as well as many domestic, professional organizations and journals (Table 2).

Table 2. Equivalency of international units

Unit	Symbol	Equivalency
Gray	Gy	1 Gy = 100 rad
Sievert	Sv	1 Sv = 100 rem
Becquerel	Bq	1 Bq = 2.7 x 10^{-11} Ci (or 1.0 disintegration per second)

Challenge

(1) A health physicist from the state health department calculates that the young boy at the scene of the accident in the case study potentially received a maximum radiation dose of 50 millirads (mrad). Express this dose in millirems (mrem) and Sieverts (Sv).

(2) What dose of X radiation would produce the same biologic effect as 50 mrad of gamma or beta radiation? If the radioactive material in the case study had been an alpha-emitter instead of a beta and gamma emitter, would the biologic effects be greater? Explain.

Exposure Pathways

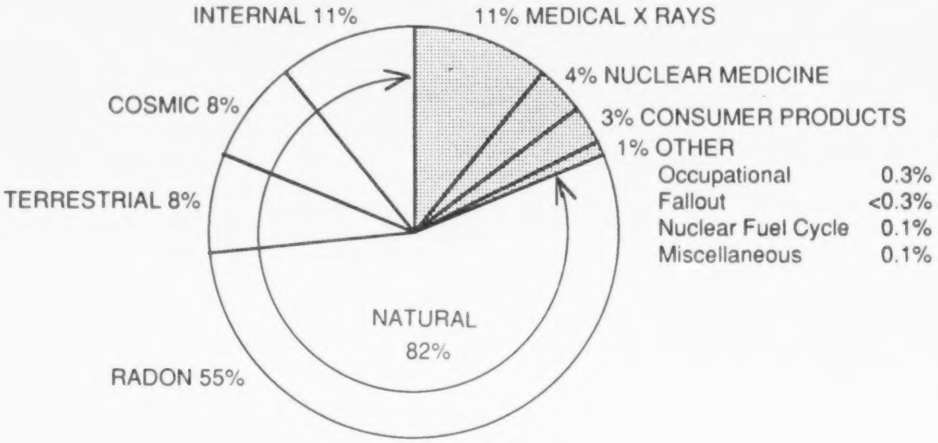
Humans receive an average radiation dose of 300 to 450 mrems per year from both natural (about 82%) and man-made (about 18%) sources. Natural radiation background (Figure 2) is from terrestrial sources and from high-energy particles emanating from stars (including our sun) and other bodies in outer space. Cosmic radiation consists mostly of protons (about 90%), with the remainder being alpha particles, neutrons, and electrons; only about 1/1000 of cosmic radiation penetrates to the earth's surface.

Near sea level, cosmic radiation results in an average dose of ionizing radiation to U.S. residents of about 30 mrem/year. At higher elevations, such as in the Rocky Mountains, where there is less atmosphere to act as a shield, exposures due to cosmic radiation increase by a factor of about two. An even greater increase is experienced during high-altitude air travel; however, passengers of commercial flights are airborne at high altitudes for only a few hours at a time and do not receive significant exposures from this source.

☐ **Our environment includes continual irradiation from both cosmic and terrestrial sources; this natural radiation background is significantly affected by altitude and geology.**

☐ **In addition to natural background, an individual's radiation exposure can be increased by factors such as lifestyle (e.g., smoking), geography (e.g., location of residence) and health requirements (e.g., medical diagnosis and therapy).**

Figure 2. Sources of ionizing radiation exposure for the U.S. population (Average annual effective equivalent dose)



Adapted with permission from *Health effects of exposure to low levels of ionizing radiation: BEIR V.* Copyright 1988 by the National Academy of Sciences. Courtesy of the National Academy Press, Washington, DC.

Terrestrial radiation comes from radioactive elements (radionuclides) that were present at the time the earth was formed, and that continue to decay, forming additional radionuclides in the process. Unusual soil composition has increased background radiation twenty-fivefold or more in a few areas in the world. Locations with high background due to naturally occurring radioactive elements in the soil, most of which are derived from the decay of uranium, include the Rocky Mountains (100 mrem/year); Kerala, India (1300 mrem/year); coastal regions of Brazil (500 mrem/year); granite rock areas of France (265 mrem/year); and the northern Nile Delta (350 mrem/year). In the United States, the lowest radiation dose rates are attributed to the sandy soils of the Atlantic and Gulf coastal plains.

One of the products formed during the decay of uranium is radon-222, an alpha-emitting radionuclide. Radon-222 contributes an average equivalent whole-body dose of about 200 mrem/year. Studies of uranium miners and other populations have indicated that inhalation of radon-222 increases the risk of lung cancer, especially in smokers. (See *Case Studies in Environmental Medicine: Radon Toxicity.*) Residents of homes built on abandoned uranium mine and mill tailings or near uranium mines, such as in the Southwest United States (e.g., Mesa County, Colorado) or in areas in Czechoslovakia, have increased internal radiation exposure due to inhalation of radon, as well as increased external radiation exposure due to uranium in the soil.

Construction materials such as wood, granite, and brick bring terrestrial radioactive sources into closer proximity. The dose rate that is attributable to the naturally occurring radionuclides in wood frame buildings is typically less than 10 mrem/year; occupants of masonry structures receive a dose rate of about 13 mrem/year. The dose rate varies not only with the material, but also with ventilation, room size, room location within the structure, season of the year, and other factors.

Potassium is essential to health, and one of its isotopes, potassium-40, is radioactive. Potassium-40 makes its way into the body through foods (e.g., bananas) and through inhaled fossil-fuel combustion products (e.g., fly-ash particulates). Because potassium deposits in muscle tissue, potassium-40 is widely distributed throughout the body. We receive an annual internal dose to all organs of approximately 18 mrem from this radionuclide.

Radiation background from man-made sources includes fallout from aboveground atomic weapon detonations (about 1 mrem/year for U.S. inhabitants), nuclear fuel production and nuclear reactors (less than 1 mrem/year), medical devices (about 50 mrem/year), and various consumer products. Although the United States and the former USSR have stopped aboveground atomic detonations, the dose rate from atomic weapons testing will continue into the next century because of the long-lived isotopes formed during previous tests and the continued aboveground testing carried out by China and France.

As of 1990, 113 nuclear power plants were operating in the United States. In addition, 75 nuclear reactors were being used for training and research, while about 70 reactors were operating at U.S. Department of Energy (DOE) facilities, and at least 100 were used to power military submarines, cruisers, and aircraft carriers. Supporting these reactors are mines, mills, processing plants, and storage sites for spent fuel, all of which are potential sources of radiation exposure. The current deposits of radioactive waste generated by production and use of atomic weapons and nuclear power reactors will remain a potential exposure hazard for 10,000 years or more.

Radiation exposure incurred for medical reasons can contribute the greatest dose from artificial sources. Worldwide, more than 1 billion medical diagnostic X-ray examinations, more than 300 million dental X-ray examinations, and about 4 million radiation therapy procedures or courses of treatment are performed annually. In the United States, over half of the population is exposed to X radiation each year, and more than half of these are diagnostic procedures, including dental diagnosis. The rest experience X radiation during fluoroscopy, radiation therapy (Table 3), and nuclear medicine (Table 4).

Table 3. Common diagnostic X-ray doses*

Examination	Mean KVP	Mean MAS (mrem)	Testes/ Ovaries (mrem)	Embryo/ Fetus
Chest (PA)	80	12	<0.5	<0.5
Skull (lateral)	72	50	<0.5	<0.5
Abdomen (KUB, AP)	78	601	13.7/146	150
Retrograde pyelogram (AP)	77	91	17.2/161	170
Thoracic spine (AP)	75	82	<0.5/0.7	0.9
Cervical spine (AP)	69	48	<0.5	<0.5
Lumbosacral spine (AP)	77	112	13.2/145	150
Pelvis (AP)	100	30	83/79	133
Barium enema (AP)	120	20	68/132	140

* KVP = kilovolt peak; MAS = milliampere second; PA = posteroanterior view; AP = anteroposterior view; mrem = millirem; KUB = kidney, ureter, bladder.

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Table 4. Common radionuclides used in nuclear medicine

Examination	Agent	mCi*	Whole body (mrem)*	Target Organ (mrem)
Lung	Technetium-99†	3	10	Lung—1000
Lung	Xenon-133 gas	15	3	Lung—150
Heart	Thallium-201 chloride	1.5	360	Kidney—2200
Heart	Technetium-99¶	15	200	Blood—300
Liver	Technetium-99§	3	60	Liver—1000
Bone	Technetium-99**	20	200	Bone—450
Kidney	Technetium-99††	10	233	Kidney—500

* mCi = millicurie, mrem = millirem
† Radionuclide delivered in microspheres of human serum albumin
¶ Radionuclide incorporated in red blood cells
§ Radionuclide delivered as sulfur colloid
** Radionuclide incorporated in methylene diphosphonate
†† Radionuclide incorporated in diethylenetriaminepentaacetic acid (DTPA)

Adapted with permission from the August, 1987; volume 36, number 2, issue of *American Family Physician*, published by the American Academy of Family Physicians.

In contrast to environmental exposures, medical procedures usually restrict radiation to local areas. However, during the course of exposing only a small fraction of the body, relatively large doses may be delivered to the bone marrow, which, in comparison to other parts of the body, is very sensitive to radiation. Although the risks due to radiation exposure are small for patients undergoing medical treatments, the cumulative risk to medical and dental personnel who are present is greater. In addition, staff who are not properly protected may receive whole-body, rather than localized, exposures. Procedures that can be used to protect health care personnel include limiting the time of exposure, maintaining an adequate distance between the X-ray beam and personnel, and providing adequate shielding.

A number of natural and artificially produced radioactive materials are used in consumer products. Of these, tobacco products probably represent the single greatest radiation hazard to smokers. Tobacco smoke contains polonium-210 and lead-210, alpha-emitting radon decay products. These radionuclides may be deposited and retained on the large, sticky leaves of tobacco plants or may derive from the uranium naturally present in the phosphate fertilizers used on the plants. When the tobacco in a cigarette is lit, the radioactive materials are volatilized and enter the lungs. The bronchial lining of the lungs of a person who smokes 1.5 packs of cigarettes per day may receive as much as 16,000 mrem/year (Table 5). The radiation from tobacco smoke may contribute to the carcinogenicity associated with active and passive cigarette smoking.

Although radiation values for dental porcelain and eyeglasses (Table 5) are large, these sources are not a health hazard because the radiation they produce is distributed over a few millionths of an inch in comparatively insensitive tissues; the total contribution of dental porcelain and eyeglasses as an equivalent *whole-body* dose is less than 5 mrem/year.

Table 5. Background radiation from consumer products

Product	Local Dose (mrem/year)	Portion of Body Considered
Coal combustion (fly ash)	0.03 - 0.3	lungs
Oil combustion (soot)	1.6	lungs
Gas ranges (natural gas)	5	lungs
Tobacco products[*]	16,000	lungs
Dentures and crowns[†]	700	superficial layers of tissue in contact with teeth
Ophthalmic glass[¶]	4,000	cornea
Smoke detectors	0.008	whole body

[*] Dose for cigarette smokers only; does not include doses experienced by those subjected to passive smoke.
[†] Due to the uranium present in glazed dental porcelain.
[¶] Applies to eyeglasses tinted with uranium or thorium.

Adapted from: National Council on Radiation Protection and Measurements (NCRP). Radiation exposure of the U.S. population from consumer products and miscellaneous sources. Bethesda, Maryland: NCRP, 1988. NCRP Report No. 95.

Challenge

(3) List at least five potential sources of radiation unrelated to the workplace to which the truck driver in the case study may be exposed. Compare the annual dose from each of these sources.

Who's at Risk

☐ **Workers in the nuclear energy and defense industries are at greatest risk of exposure to ionizing radiation.**

☐ **Accidental releases of radiation can occur while producing, using, storing, or transporting radionuclides.**

☐ **Long-term sequelae of acute high-level or low-level radiation (i.e., cancer and genetic effects) are difficult to assess for a number of reasons.**

Important data about human effects from exposure to ionizing radiation come from survivors of the atomic bomb detonations in Hiroshima and Nagasaki. Additional evidence comes from inhabitants of the Marshall Islands who experienced fallout from thermonuclear testing on Bikini Atoll, radium dial painters, pioneer radiologists, and patients receiving radiation therapy (e.g., patients who were irradiated in the 1950s as treatment for ankylosing spondylitis). Effects of high-level exposure include acute radiation sickness and fatalities. The major long-term health risks of ionizing radiation are cancer, birth abnormalities (from in utero irradiation), infertility, and genetic abnormalities, which are discussed in *Physiologic Effects*, page 13.

Risk of radiation-induced cancer in human populations is difficult to calculate for four reasons: (1) the total number of known radiation-induced cases is too small and the doses too high to allow accurate extrapolation to low doses; (2) cancer from other causes is a prevalent disease (the incidence of cancer morbidity in the U.S. population is 30% to 35%), making incremental incidences due to radiation exposure difficult to detect; (3) radiation-induced cancer cannot be distinguished from cancer due to other causes (although investigators using new molecular biology techniques are attempting to make this distinction possible), and (4) the interval between radiation exposure and cancer appearance may be several decades.

Exposure to low-level ionizing radiation occurs mostly in the workplace. Workers at risk are those involved in the following activities: operating nuclear power plants, other nuclear industrial facilities, or nuclear-powered naval vessels; purifying, enriching, and fabricating uranium for nuclear reactor fuel and for weapons production and use; and working at radionuclide storage sites. In addition, medical technicians; researchers; uranium miners and other underground miners, cave guides, and spelunkers exposed to radon; industrial radiographers; and geologists using radiologic devices to measure pressure in wells are at risk of radiation exposure.

Criticality accidents (due to uncontrolled nuclear fission) have occurred at Los Alamos, New Mexico, in 1958; Oak Ridge, Tennessee, in 1958; Hanford Works, Richland, Washington, in 1962; and Wood River Junction, Rhode Island, in 1964. In addition, two early experiments (in 1945 and 1946) at the Los Alamos site resulted in uncontrolled nuclear fission. These accidents caused three early fatalities of workers closest to the nuclear reactions; the 22 other workers in the vicinity of the accidents were irradiated at doses less than 465 rem, and all survived for at least 5 years. The radiation from these accidents would have affected a larger area and a greater number of people if conditions during criticality had also resulted in the explosive release of large amounts of energy, which they did not.

The general public can be exposed to radiation through industrial or mining waste streams that contaminate air and drinking water. Releases of iodine-131 to air and water occurred at nuclear power plants in Hanford, Washington, during the period from 1943 to the 1960s and at Three Mile Island in 1978. The release of radioactivity at the Three Mile Island nuclear power plant resulted in an average radiation dose to the surrounding population of about 8 mrem over a radius of 10 miles and about 2 mrem over a radius of 50 miles from the reactor. These doses are conservatively expected to cause an additional 0.7 cancer deaths in the population living within the affected 50-mile radius. (By contrast, the number of cancer deaths estimated to occur from all other causes during the lifetime of this population of 2 million persons is about 390,000.)

Accidental releases of radioactive materials may also occur during transport of radionuclides or at sites storing them. Currently, low-level radioactive waste can be accepted at two commercial storage sites: Barnwell, South Carolina, and Hanford, Washington. The storage site at Beatty, Nevada, no longer accepts shipments of radioactive waste. No repository has yet been designated as a permanent storage site for high-level radioactive waste such as spent fuel from nuclear reactors.

ATSDR

Biologic Fate

☐ **Depending on their physical state, radionuclides may enter the body by ingestion, inhalation, or by absorption through the skin. They may also enter the body through breaks in the skin.**

☐ **Distribution, metabolism, and excretion depend on the radionuclide and its chemical form.**

☐ **Radium and transuranic radionuclides may remain in the liver and bone for years.**

Exposure to ionizing radiation can result from internal sources (i.e., radionuclides deposited within the body), external contamination (i.e., radionuclides deposited on the body surface), and irradiation by an external source. Internally deposited radionuclides frequently produce nonuniform radiation to proximate organs and tissues, depending on the radionuclide's distribution and metabolic characteristics. In many respects, internal contamination can be viewed as chronic exposure.

Radioactive substances can enter the body via inhalation, ingestion, skin absorption or through a contaminated wound. Inhalation is the most common route of internal contamination. Depending on particle size, aerosols may penetrate beyond the self-cleansing mucocilliary system of the central airways. For insoluble aerosols, such as oxides of plutonium and other transuranic elements (elements having an atomic number greater than uranium), the biologic fate usually includes transfer of the radionuclide by macrophages to regional lymph nodes and partial solubilization, with entry into the circulatory system. Heavy nuclides remain in the liver and bone for prolonged periods, typically years.

Hundreds of radioactive nuclides exist, but only a few are extensively used or produced and have the potential to cause significant internal contamination. The radionuclides in the environment of greatest potential concern are cesium-137, iodine-131, plutonium-239, radon-222, strontium-90, tritium, and uranium-238. A brief discussion of the biologic fates of each of these radionuclides can be found in *Appendix II*.

Challenge

Additional information for the case study: The radioactive material has been identified as an aqueous solution of potassium iodide, which was prepared from iodide-131. The cargo was being delivered to a repository for storage of low-level radioactive waste.

(4) Several hours after the accident occurred, a fireman who was first-on-scene is brought to the emergency room complaining of mild chest pain. He asks you if this pain could be caused by radioactivity in the smoke. Considering the biologic fate of iodide-131, is this a likely cause of the patient's chest pain? Explain.

Physiologic Effects

The immediate effect of exposure to high-level ionizing radiation is cytotoxicity, which results in changes in cellular function or direct cell death. Changes in cellular function may include delays in certain phases of the mitotic cycle (mitotic inhibition), disrupted cell growth, permeability changes, and changes in motility.

A suggested mechanism for radiation cytotoxicity involves the formation of ions, which interact with water and create inhibitory toxic chemicals (e.g., hydrogen peroxide) and free radicals that destroy the integrity of proteins, DNA, or other cellular constituents. The body's response to ionizing radiation depends on several factors, including the type and quality of radiation, dose, dose rate, and homogeneity of dose. If a cell receives a sublethal dose of radiation, cellular repair processes may be activated. Repair mechanisms are most likely responsible for the ability of the body to tolerate a higher total dose when exposure occurs over an extended period of time (i.e., at a low dose *rate*).

Cytotoxicity from radiation varies among cell types and tissues. In general, rapidly dividing cells that are poorly differentiated are most radiosensitive. For example, lymphocytes, primitive stem cells of the bone marrow, mucosal crypt cells of the gastrointestinal tract, spermatogonia, and granulosa cells of the ovary are particularly affected by radiation. Endothelial cells of the microcirculation and epithelial cells of many organs have an intermediate sensitivity. Muscle cells, neurons, erythrocytes, and polymorphonuclear granulocytes are relatively resistant to radiation. In most cases, maximum organ damage becomes evident as injured progenitor cells fail to replace the lost mature cells.

☐ **Rapidly dividing cells are the most sensitive to ionizing radiation.**

☐ **Hemopoietic changes become observable at exposure levels of about 25 to 100 rem. Changes in the function of most other cells or immediate cell death occurs at exposure levels greater than 100 rem.**

☐ **DNA repair mechanisms likely influence the effects of radiation exposure that has occurred over an extended period of time.**

Cancer

The largest body of evidence in support of the ability of ionizing radiation to produce cancer derives from studies of the survivors of the atomic detonations during World War II. The increased rates of various cancers in those persons are consistent with the increased rates for comparable cancers in other irradiated populations. A radiation dose of 100 rem causes about a 5% increase in the risk for developing a fatal cancer. Risk of some cancers (e.g., female breast cancer and multiple myeloma) more than doubles with exposure doses greater than 100 rem. A reasonable estimate of additional cancer mortality risk from a one-time whole-body dose of 1 rem is 1 to 5 fatal cancers in 10,000 persons so exposed (0.01% to 0.05%). This risk is in addition to the cancer mortality risk in the general U.S. population of about 1950 fatal cases in 10,000 persons (19.5%).

The first radiation-induced malignancy to appear in the atomic bomb survivors was leukemia. The latent period between radiation exposure and clinical recognition of leukemia ranged from 2 to 15 years.

☐ **Large doses of ionizing radiation will significantly increase the incidence of cancer in a population. However, at low doses, the incidence of radiation-induced cancer is difficult to detect.**

The risk to the survivors of developing this disease varies with the type of leukemia and the age at the time of exposure. For example, the incidence of chronic lymphocytic leukemia (CLL) is not measurably affected by the radiation level or dose, whereas the incidence of all other types of leukemia has been reported to increase with dose, and the risk is greater to those who were exposed at a younger age.

In the Japanese survivors, increased incidences for solid cancers appeared considerably later than the excess of leukemia. Carcinoma of the thyroid was the first of the solid tumors noted. An increased incidence of multiple myeloma and cancers at the following sites was also found: breast (female), lung, stomach, esophagus, small intestine, colon and rectum, brain and nervous system, ovary, uterus, urinary tract, and salivary glands. In populations irradiated occupationally or primarily for medical reasons, an increased incidence of cancers at these sites has also been reported, as well as at other specific sites including liver [due to internally deposited radionuclides], skeleton, and skin. Current medical reagents and procedures in nuclear medicine are designed to minimize residual radionuclides in the body and adverse side effects.

As with leukemia, the risks for solid tumors in the Japanese survivors are greater in persons who were younger at the time of exposure. The latency period for solid tumors due to radiation exposure is generally one or more decades. Interestingly, an increase in pancreatic cancer, the fourth leading type of fatal cancer in the United States, was not observed in atomic bomb survivors and has been observed inconsistently in other irradiated human populations (i.e., no clear relationship to dose or time after exposure could be identified).

Developmental Effects

☐ **The fetus, with its rapidly dividing cells, is especially radiosensitive.**

Exposure of pregnant women to ionizing radiation has been studied in several populations including survivors of the atomic bomb detonations in Japan. Preimplantation radiation exposure (i.e., within 2 weeks after conception) has not been found to produce anomalies in the fetus. If preimplantation damage occurs, it is likely that spontaneous abortion ensues. In women exposed during pregnancy, increased incidences of miscarriages, stillbirths, and neonatal deaths have been reported. Children exposed in utero have shown an excess of congenital defects.

In children born to survivors of the atomic bomb detonations, a pronounced association exists between gestational age at the time of exposure and the risk of neurodevelopmental effects. Exposure occurring during the first 7 weeks of gestation did not result in increased risks for mental retardation, reduced IQ, or seizure disorders. Exposures greater than 50 rad during gestational weeks 8 to 15, when nerve development and migration are greatest, showed linear dose-effect relationships for each of the above three endpoints and for microcephaly. This gestational period (i.e., 8 to 15 weeks) is recognized as the most sensitive for the development of fetal neurologic effects (see *Case Studies in Environmental Medicine: Reproductive and Developmental Hazards*). A no-effect threshold for adverse neurodevelopmental effects during this gestational period could not be determined.

Exposures that occurred during 16 to 25 weeks of pregnancy also resulted in an increased risk of adverse neurodevelopmental effects, but to a lesser degree than during the period of peak sensitivity. Irradiation during the 16th to 25th week did not produce a linear relationship between dose and effect. In fact, a threshold for mental retardation appeared to exist. After 25 weeks of gestation, radiation exposures generally cause stunting of growth in the fetus, resulting in a newborn who has reduced physical size but remains normal in other ways.

Genetic Effects

In nonhuman forms of life, the developmental and genetic effects of ionizing radiation are well documented. Radiation exposure in these life forms results in congenital abnormalities and mutations that are transmitted to immediate and remote offspring. In experimental animals, the frequency of genetic effects due to radiation exposure generally increases as a linear-nonthreshold function of dose.

- ☐ **Genetic effects due to ionizing radiation are well documented in animals and other nonhuman forms of life.**
- ☐ **Although inheritable defects have not been evident in atomic bomb survivors, no reason exists to assume that humans are exempt from radiation-induced genetic effects.**

An epidemiologic study in Japan compared 38,000 children conceived after one or both parents were exposed to radiation from atomic detonations with 37,000 children whose parents were not exposed. No statistically significant differences were found in stillbirths, birth weight, infant mortality, or sex ratio. Among children of the exposed parents, there was also no effect seen on electrophoretic variants of 28 proteins of blood plasma and erythrocytes. These results may be due to relevant factors that were not controlled in the study. Although this study was negative, it does not prove that humans are exempt from radiation-induced genetic effects.

The dose needed to double the mutation rate in humans has been calculated to be higher than 100 rem, which is twice the average gonadal dose received by the atomic bomb survivors. Although the children of the survivors exhibited no inherited chromosomal abnormalities, the survivors themselves showed a dose-dependent increase in chromosomal abnormalities in somatic cells (i.e., circulating blood lymphocytes), which has also been detected in other populations exposed to ionizing radiation.

Some studies involving women who have had medical X-ray exposures suggest an association between maternal preconception exposure to ionizing radiation and the incidence of Down syndrome, while others do not. Thus, the studies are inconclusive. A similar paternal radiation effect has not been noted. Children whose parents received preconception exposures of greater than 1 rem at Hiroshima and Nagasaki have not exhibited increased incidences of Down syndrome, leukemia, or non-Hodgkin's lymphoma.

Challenge

Additional information for the case study: The boy is located with friends several hours after the accident and taken to the emergency department of the local hospital. He says he did not come in contact with the radioactive material.

(5) Is the boy a hazard to those with whom he has come in contact since the accident? Explain.

(6) Is the boy, the truck driver, or his assistant at increased risk of cancer? Explain.

Clinical Evaluation

Acute Radiation Syndrome

Approximately half of those receiving a radiation dose of 500 rem will die within 30 days if untreated. Below 1000 rem, deaths are attributable to failure of the hematopoietic system. For doses between 1000 and 10,000 rem, death occurs due to ulceration and bleeding in the gastrointestinal tract. Doses above 10,000 rem immediately affect the cells of the nervous system. Depending on the exposure dose, these subsyndromes (i.e., hematopoietic, gastrointestinal, and neurovascular), which make up the acute radiation syndrome, may be discrete or overlapping (Table 6).

- ☐ **No immediate symptoms occur from acute doses of whole-body radiation below about 100 rem.**
- ☐ **The acute radiation syndrome consists of subsyndromes involving the hematopoietic, gastrointestinal, and neurovascular systems.**

Table 6. Acute effects of whole-body doses of ionizing radiation

rem*	
0 - 25	No detectable clinical effects; small increase in risk of delayed cancer and genetic effects
25 - 100	Temporary reductions in lymphocytes and neutrophils; sickness not common; long-term effects possible
100 - 200	Minimal symptoms; nausea/vomiting/diarrhea/fatigue in a few hours; reduction in lymphocytes and neutrophils, with delayed recovery; possible bone growth retardation in children
200 - 300	Nausea and vomiting on first day; following latent period of up to 2 weeks, symptoms (loss of appetite and general malaise) appear but are not severe; hematopoietic subsyndrome; recovery likely in about 3 months unless complicated by previous poor health
300 - 600	Nausea, vomiting, and diarrhea in first few hours, followed by latent period as long as 1 week with no definite symptoms; loss of appetite, general malaise, and fever during second week, followed by hemorrhage, purpura, inflammation of mouth and throat, diarrhea, and intestine destruction in third week; some deaths in 2–6 weeks; possible eventual death to 50% of those exposed
600 - 1000	Vomiting in 100% of victims within first few hours; diarrhea, hemorrhage, and fever toward end of first week; rapid emaciation; almost certain death
1000 - 5000	Vomiting within 5–30 minutes; 100% incidence of death within 2–4 days
>5000	Vomiting immediately; 100% incidence of death within a few hours to 2 days
Also	
>15	In men yields temporary sterility
>300	In women yields permanent sterility

*rem = rad equivalent in man or mammal

Adapted from: Goldman M. Ionizing radiation and its risks. In: Occupational disease—new vistas for medicine. West J Med 1982;137:540-7.

Acute radiation illness begins with a prodromal period manifesting within hours or a few days. Prodromal symptoms include anorexia, nausea, vomiting, and diarrhea. A latent period of 5 to 7 days then occurs during which the patient appears to have recovered. Within 2 weeks after exposure, the patient will manifest illness that requires aggressive therapy; this critical period may last up to 4 weeks. Generally, the higher the absorbed dose, the shorter the latent period and the more rapid the onset and severity of illness during the critical period.

At levels above 100 rem whole-body dose, radiation-sensitive stem cells in the bone marrow and lymphoid tissues are destroyed or mitotically impaired. The more radio-resistant mature elements normally circulating in the blood cannot be replaced promptly, and fatal hemorrhage can result from platelet loss. Infection from decreased production of granulocytes and other cells can also occur. Recovery has been reported after exposure to 300 to 600 rem when intensive supportive care was provided. Erythrocyte production is also decreased, but in the absence of bleeding, anemia develops only slowly and in modest severity because erythrocytes have a long life span.

Acute radiation doses exceeding 600 rem to the abdomen or whole body usually result in significant damage and reproductive impairment of rapidly proliferating crypt stem cells, thus producing the gastrointestinal tract subsyndrome. The existing mucosa is shed, preventing normal absorption and causing the gut to leak electrolytes and blood. The denuded mucosa becomes a portal of entry for intestinal bacteria; severe diarrhea, shock, and sepsis occur. Although medical therapy may delay death from these causes, the patient usually succumbs.

Acute doses of more than 3000 rem cause damage to capillaries, resulting in a more immediate neurovascular subsyndrome. Within 1 hour after exposure, neurologic symptoms of confusion, prostration, and loss of balance develop. Diarrhea, respiratory distress, intractable hypotension, and central nervous system (CNS) collapse rapidly ensue. Massive damage to the microcirculation probably is responsible for the cerebral edema that causes brain damage. The initial hypotension may be due to release of histamine by the granulated mast cells. At this radiation dose, medical efforts are futile, and death occurs within 48 hours after exposure.

Local Radiation Injury

In a radiation accident, high local exposures may complicate whole-body exposures. Since 1945, about 300 radiation accidents have occurred in the United States, the majority of which have involved industrial devices containing cobalt-60 or iridium-192. Injury to the skin depends on the type of radiation, as well as the strength of the source and duration of the contact. For example, beta radiation typically produces a shallow injury, whereas gamma radiation penetrates more deeply. Both cobalt-60 and iridium-192 are gamma emitters and can produce contact doses that result in immediate and severe third-degree burns. Third-degree contact burns are generally painless and actual skin damage may be worse than is immediately apparent. Most local injuries involve the hand; other common sites are the thighs and buttocks when radioactive sources are carried in pants' pockets. The acute radiation syndrome may also be present in patients who have severe local contact injury.

☐ **Contact with a radioactive source can result in burns that are worse than is immediately apparent.**

☐ **Most local radiation injuries involve the hands.**

The intensity of radiation from a source decreases as the distance from the source increases, in accordance with the "inverse square" rule. For example, a dose of 1024 rads at 1 meter from a source is reduced to 256 rads at 2 meters and 64 rads at 4 meters. If the immediate signs and symptoms after a local radiation exposure include erythema of skin and severe pain, the local absorbed dose is probably in excess of 1000 rads. Evidence of transepithelial injury and dry desquamation may follow. At doses above about 2000 rads, blistering and a wet radiodermatitis may ensue. Later, tissue necrosis due to secondary vascular impairment may occur. These injuries are similar to thermal burns in appearance. In radiation cases, erythema may increase during the first week after exposure and fade during the second week but may recur. A feeling of tenderness and itching usually persists.

Laboratory Evaluation

External Indicators

Instruments used to measure radiation levels in the environment are generally of two types: area survey meters and personnel dosimeters. If either dosimetry is available, contact a health physicist for interpretation. These radiation experts are employed at local or state departments of health, universities, and the Radiation Emergency Assistance Center/Training Site (REAC/TS) at Oak Ridge Institute for Science and Education (see *Other Sources of Information*, page 29).

☐ **An accurate assessment of radiation dose is a useful, though not essential, confirmatory aid to clinical judgment in treating severely affected patients.**

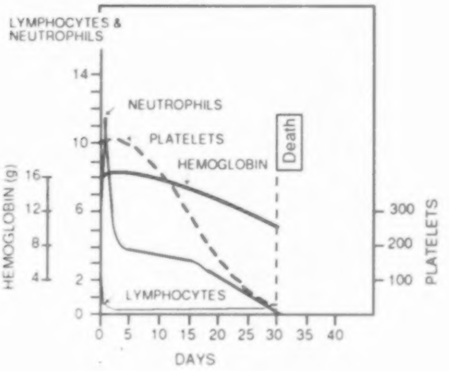
Internal Indicators

If whole-body radiation has occurred, several hematologic parameters can be used to predict biologic effects, as well as to estimate physical dose. The earliest indicator is a fall in the lymphocyte count, which may reach its nadir within 48 hours (Figure 3). At doses up to

☐ **Lymphocytes are a biologic marker for radiation exposure.**

300 rad, the rate of fall in circulating lymphocytes is related directly to dose. At doses greater than 300 rad, profound lymphocytopenia occurs, and lymphocyte count becomes unreliable for dose estimation.

Figure 3. Typical hematologic response* to a whole-body radiation dose of 450 rads



* Lymphocyte, neutrophil, and platelet values should be multiplied by 1000. Hemoglobin values are in grams per deciliter.

Adapted from: Goldman M. Ionizing radiation and its risks. In: Occupational disease—new vistas for medicine. West J Med 1982;137:540-7.

Unlike lymphocytes, granulocytes (represented by neutrophils in Figure 3) are not directly lysed by radiation and provide another indication of dose. At whole-body doses of 200 to 500 rads, a brief rise in the peripheral granulocytic count typically occurs in the first few days after exposure. The rise, which is a nonspecific stress response, is followed by a progressive fall, an abortive rise or plateau, and another fall, the true nadir of which is reached within 30 days after exposure. Doses greater than 500 rads cause increasingly earlier and more severe granulocytopenia. The severity of thrombocytopenia (see platelets in Figure 3) is also an indicator of dose.

A useful and sensitive biomarker for dose estimation in acute whole-body radiation exposures, as well as to predict the long-term health risks in large populations exposed to low levels of radiation, is the chromosome aberration assay. Radiation induces several nonspecific but characteristic chromosomal abnormalities, particularly dicentric chromosomes. By scoring the frequency of these abnormalities in lymphocytes in the peripheral blood or bone marrow and comparing the frequency to aberrations produced by irradiating peripheral blood in vitro, a relatively accurate estimation of radiation dose can be made. Chromosomal aberrations are visible within hours after radiation exposure, and the optimum time to perform the assay is within the first few weeks after exposure. Details of sample preparation and the names of laboratories able to perform cytogenetic assays for radiation exposure can be obtained from REAC/TS (telephone: [615]-576-3131 [day]; [615] 481-1000 [24-hour hotline]).

Indicators of internally deposited radionuclides will depend on the biologic fate and the biologic half-life of the radioactive substance. If the metabolic pathway and biologic and physical half-lives are known, an estimate of dose to the target organ can be made by bioassay. Methods for measuring the amount of radioactivity in the body include urinalysis, fecal analysis, whole body scans, and thyroid scans for exposure to radioactive iodine.

Cytogenetic assays may also be used to detect damage from internally deposited radionuclides. However, these data are not useful in estimating dose to the target organ because internal radionuclides are seldom distributed uniformly within the body. This uneven distribution can affect the radiation received by the circulating lymphocytes and even their survival.

Challenge

(7) About 36 hours after arriving at the emergency department, the driver in the case study and his assistant experience nausea and vomiting. What is the prognosis for these patients?

____

____

(8) In the emergency room you have an opportunity to examine the young boy. What history or other information will help you determine his prognosis?

____

____

(9) One month later, the boy's parents ask you to perform a test that will prove the boy was exposed to radiation. Is this possible? Explain.

____

____

Treatment and Management

Early Considerations—Decontamination

- ☐ **An important consideration in decontamination is to prevent the spread of radioactive materials.**
- ☐ **The psychologic effects of actual or potential radiation exposure are often overlooked.**

If radioactive materials are present in a workplace, it is important to have decontamination materials available and a written plan for their utilization. Radiation detection equipment is used to identify a worker contaminated with radioactive liquids or solids (e.g., dusts), as well as the body area that is contaminated.

The first step in decontamination is removal of contaminated clothing, then careful washing of the areas around eyes, nose, and mouth with a washcloth. Showering should be avoided when external contamination is localized because showering can spread radionuclides to clean areas. Mild soap and water are frequently all that is needed to emulsify and remove contamination. Gentle brushing or use of a mildly abrasive soap will help dislodge contamination physically held by skin protein. Harsh abrasives should be used cautiously because they may open a path through the keratinized layer of the skin and allow internal contamination. Addition of a chelating agent to the wash water may help by binding the radionuclide in a complex. Contaminated wash water must be collected and disposed of properly. Instructions for disposal can be obtained from REAC/TS (telephone [615]-576-3131 [day], [615] 481-1000 [24-hour hotline]).

Radiation monitoring of the cleaned, dried skin should be done between washings. If repeated washings do not totally remove contamination, the material is probably fixed in skin, which will normally be shed; a frequently changed bandage over the area will prevent spread of contamination via the sloughed skin. In stubborn cases where contamination is localized in the thick horny layers, such as palms and soles of feet, sticky tape or a high-speed abrasive wheel can be used. However, if these techniques are not used properly, they can lead to skin cuts or increased percutaneous absorption. It may be necessary to remove contaminated hair by using clippers or an electric razor. All potentially contaminated material, including hair, debrided tissue, and, if internal contamination has occurred, vomitus and excretion products, must be collected in plastic bags for proper disposal.

If the contaminated worker is physically traumatized, the emergency department plan for management of radiation-accident casualties should be executed. Lifesaving medical care takes precedence over decontamination procedures. After emergency care has been administered, gross decontamination should be conducted on site. Further decontamination can occur at the medical facility. The patient should be wrapped in blankets to prevent the spread of contamination during transport. If the medical facility is not prepared for radiation decontamination and does not have an appropriate decontamination room, the patient should be decontaminated outside or away from areas where normal activities occur. Care must be taken to prevent the spread of radioactivity within the facility.

The general public perceives the risk of death or injury from radiation as greater than do scientists. Dealing with the fear and mental stress caused by an accident is a significant part of emergency management. Techniques for combatting this anxiety include educating the public before an emergency occurs, efficiently disseminating factual information using a single credible source during the emergency, and presenting evidence that a plan to manage the emergency is in place and working.

Acute Radiation Syndrome

Patients who have received acute total body radiation of 500 rads or more will develop severe pancytopenia and will require aggressive supportive measures. Patients developing aplastic anemia are at risk for systemic bacterial, fungal, and viral infections; infections and bleeding are the major causes of morbidity and mortality. Clinicians are encouraged to consult a hematologist, radiation oncologist, health physicist, or other radiation specialist knowledgeable about acute radiation illness and its treatment. Some referral sources are given in *Other Sources of Information*, page 29. A general treatment scheme for acute radiation injury is presented in Figure 4.

- ☐ **Bleeding and infections, which are the primary causes of morbidity and mortality in patients acutely exposed to radiation, should be promptly treated by specialists.**

Local Radiation Injury

Radiation exposures that produce only erythema (300-1000 rad) can be treated as first-degree burns. Burns that result in desquamation (1000-2000 rad) are transepidermal and are similar to second-degree burns. Large surface-area burns may require systemic hydration. Skin grafting may be useful, but success depends on the depth of radiation penetration and the vascular status of the underlying tissues. Third-degree burns are produced by doses greater than 3000 rad. Third-degree burns heal by scarring; as a result, contraction and loss of function may occur, particularly if extremities are involved. Extensive plastic surgery may be required to prevent or limit loss of function. Amputation may be necessary.

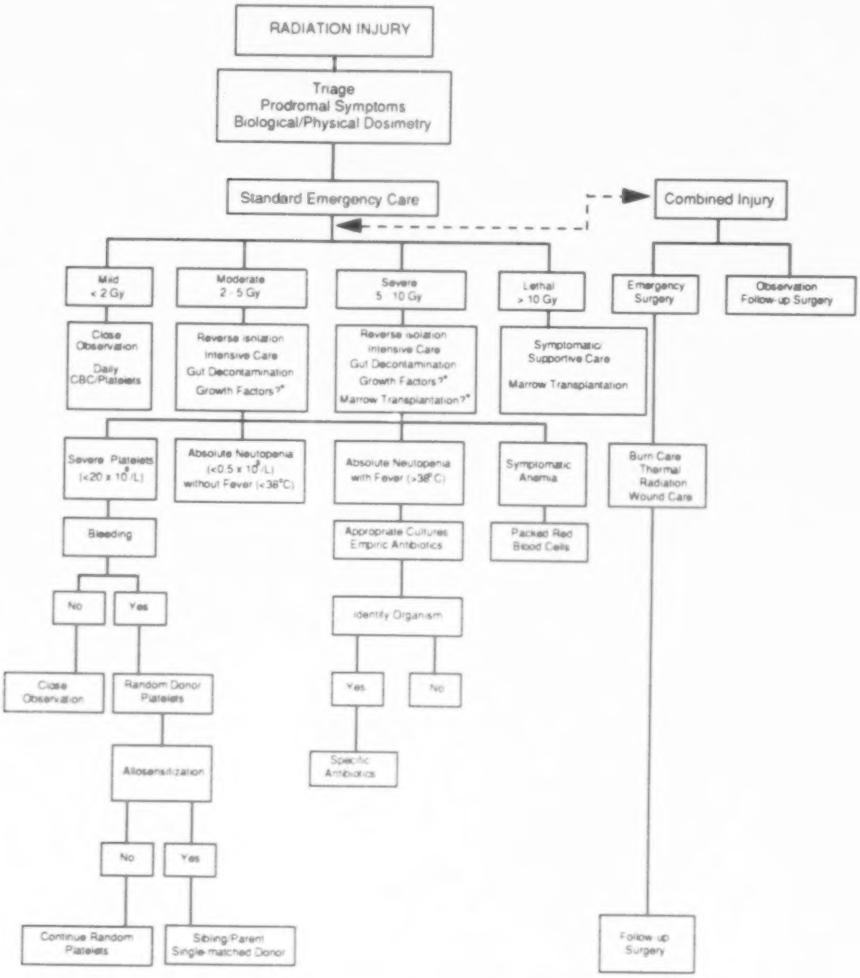
- ☐ **Treatment depends on the area of the burn and the depth of radiation penetration.**

Internal Contamination

Two strategies exist for treatment of a patient who is internally contaminated (i.e., cases where radioactive material is incorporated in the body via inhalation, ingestion, or through skin or wounds). The first strategy depends on reducing both the internal absorption and deposition of radioactive material ("blocking"); the second strategy depends on enhancing the elimination and excretion of the radioactive material ("decorporation").

- ☐ **Generally, treatment strategies involve reducing internal absorption and enhancing elimination.**

Figure 4. Treatment scheme for patients receiving an acute high-dose radiation exposure


RADIATION INJURY
Triage
Prodromal Symptoms
Biological/Physical Dosimetry
Standard Emergency Care
Combined Injury
Mild
< 2 Gy
Moderate
2 - 5 Gy
Severe
5 - 10 Gy
Lethal
> 10 Gy
Emergency Surgery
Observation
Follow-up Surgery
Close Observation
Daily CBC/Platelets
Reverse isolation
Intensive Care
Gut Decontamination
Growth Factors?*
Reverse isolation
Intensive Care
Gut Decontamination
Growth Factors?*
Marrow Transplantation?*
Symptomatic/
Supportive Care
Marrow Transplantation
Severe Platelets
($<20 \times 10^9$/L)
Absolute Neutopenia
($<0.5 \times 10^9$/L)
without Fever (<38°C)
Absolute Neutopenia
with Fever (>38°C)
Symptomatic Anemia
Burn Care
Thermal
Radiation
Wound Care
Bleeding
Appropriate Cultures
Empiric Antibiotics
Packed Red Blood Cells
No
Yes
Identify Organism
Close Observation
Random Donor Platelets
Yes
No
Specific Antibiotics
Allosensitization
No
Yes
Continue Random Platelets
Sibling/Parent
Single-matched Donor
Follow-up Surgery

* Whole-body exposures greater than 4 Gy may require bone marrow transplantation or administration of colony-stimulating factors or other hematopoietic growth factors that stimulate proliferation of hematopoietic stem cells. However, few data exist to support firm recommendations about the use of these treatments for radiation victims.

Adapted from: Browne D, Weiss JF, MacVitlie TJ, Pillai MV. Treatment of radiation injuries. New York: Plenum Press, 1990.

In radiation accidents, the identity of the radionuclide contaminant and its chemical and physical state must ultimately be determined. Radionuclides present at a workplace are usually known, and shipping documents and load manifests detail the hazardous contaminants at transportation accidents. Sometimes it will not be clear whether internal contamination has occurred. Samples collected during external decontamination will provide clues about possible internal contamination. Skin wipes, nasal swabs, urine, and feces should be collected for analysis at a laboratory capable of detecting and identifying radionuclides. Local and whole-body counting can be done at specialized facilities. As mentioned above, gentle mechanical cleansing of wounds and skin and the areas around mouth and nose will prevent further ingestion and absorption of radioactive materials.

☐ **Treatment of a patient who is internally contaminated is specific to the contaminating radionuclide and chemical form.**

Chelation with diethylenetriaminepentaacetic acid (DTPA) accelerates the urinary excretion of some transuranic metals (e.g., plutonium, californium, americium, and curium) and some rare earth ions (e.g., cerium, yttrium, lanthanum, promethium, and scandium). DTPA is an investigational drug available from REAC/TS (see *Other Sources of Information*, page 29). DTPA can be administered intravenously or as an inhaled aerosol according to treatment protocols established by investigators at REAC/TS. In rare cases of massive pulmonary deposition of very hazardous aerosolized radionuclides, lung lavage may be of value. *Appendix II* is a treatment summary for selected elements.

Challenge

(10) How will you manage and treat the truck driver and his assistant in the case study? Assuming the young boy has experienced no immediate effects from the irradiation, what follow-up is appropriate for him?

Additional information for the case study: An hour after the accident, the concentration of radioactivity at the point where the material entered the river was measured at 20 picoCuries per liter (pCi/L) of river water. The town switched to an alternate source of drinking water. Two weeks later, the state public health department declared the river water safe, and the town resumed using the river as its source of drinking water.

(11) You continue to receive calls from your patients, expressing fear and concern about exposure to radioactivity. One of these patients insists that a rash that developed on his arm yesterday is caused by showering with "radioactive water." A patient who is pregnant fears that her unborn child will be malformed or have cancer as a result of her drinking water from the river. How will you respond?

ATSDR

Standards and Regulations

During the period 1900 to 1930, standards for radiation protection were informal and set quite high (approximately 60 R/year). They reflected concern for acute effects of exposure. When concerns over the long-term effects of radiation exposure began to develop (1930 to 1950), protection standards were formalized. The recommendation in 1934 of the U.S. Advisory Committee on X-Ray and Radium Protection (now the National Council on Radiation Protection and Measurements [NCRP]) was to restrict whole-body exposures to less than 0.1 R/day. From 1950 to 1960, attention centered on genetic effects of radiation exposure, and recommendations were proposed to limit exposure to the equivalent of 5 rem/year, which applied to both the general public and workers. Because any amount of radiation exposure poses some risk, all standards now employ a philosophy that radiation exposures should be limited to levels that are as low as reasonably achievable (ALARA) and consistent with the benefits of radiation to society.

Regulatory agencies in the United States that are involved in radiation control include the Nuclear Regulatory Commission, Department of Transportation, Food and Drug Administration, Occupational Safety and Health Administration, and the General Accounting Office. EPA has also established a standard for drinking water of 5 pCi/L, which applies to radioactivity from radium-226 and radium-228 combined. A new drinking water standard of 20 pCi/L each for radium-226 and radium-228 has been proposed.

Many states and cities also have regulations concerning the use of and protection from radiation. NCRP, established in 1964 to advise Congress on issues related to radiation, and the International Commission on Radiological Protection (ICRP) recommend the standards in Table 7.

Table 7. Summary of recommendations for ionizing radiation

Dose Limits for Workers[*]	**ICRP, 1991[†]**	**NCRP, 1993[¶]**
Based on stochastic effects[§] (e.g., cancer and genetic damage)	5 rem (50 mSv) annual effective dose limit and 10 rem (100 mSv) as 5-year cumulative effective dose limit	5 rem (50 mSv) annual effective dose limit and 1 rem (10 mSv) times age in years cumulative effective dose limit
Based on nonstochastic effects[§] (e.g., lens cataracts and fertility impairment)	15 rem (150 mSv) equivalent dose limit to lens of eye and 50 rem (500 mSv) annual equivalent dose limit to skin, hands, and feet	15 rem (150 mSv) annual equivalent dose limit to lens of eye and 50 rem (500 mSv) annual equivalent dose limit to skin, hands, and feet
Dose Limits for the Public[*]	**ICRP, 1991**	**NCRP, 1993**
Based on stochastic effects	0.1 rem (1 mSv) annual effective dose limit, and, if needed, higher values provided that the annual average over 5 years does not exceed 0.1 rem	0.1 rem (1 mSv) annual effective dose limit for continuous exposure and 0.5 rem (5 mSv) annual dose limit for infrequent exposure
Based on nonstochastic effects	1.5 rem (15 mSv) annual equivalent to lens of eye and 5 rem (50 mSv) annual equivalent dose limit to skin, hands, and feet	5 rem (50 mSv) annual equivalent dose limit to lens of eye, skin, and extremities
Embryo-fetus	0.2 rem (2 mSv) equivalent dose to the woman's abdomen once pregnancy has been declared	0.05 rem (0.5 mSv) equivalent dose limit in a month once pregnancy is known

[*] The dose limits for both workers and the public exclude medical and natural background exposures. Note that the dose limits for the public are lower, in general, than those for workers. Workers, by virtue of the ability to work, tend to be a healthier population than the public, which includes susceptible populations, the elderly, and children.

[†] International Commission on Radiological Protection. 1990 Recommendations of the International Commission on Radiological Protection, ICRP Publication 60. Annals of the ICRP 21. Elmsford, New York: Pergamon Press, 1991.

[¶] National Council on Radiation Protection and Measurements (NCRP). Limitation of exposure to ionizing radiation. Bethesda, Maryland: NCRP, 1993. NCRP Report No. 116.

[§] Stochastic effects are those effects for which the probability of occurrence, rather than the magnitude of the effect, is proportional to dose. Not all irradiated persons show such effects, however, the probability that they will can be described by a dose-response curve that extends to zero with no threshold. Nonstochastic effects are proportional in severity to the magnitude of the absorbed dose; they probably have a threshold below which no effect will be observed because simultaneous injury to many cells is required.

ATSDR

Suggested Reading List

Acute High-Level Exposure

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Treatment

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National Academy of Sciences. Medical implications of nuclear war. Washington, DC: National Academy Press, 1986.

Other Sources of Information

More information on the adverse effects of ionizing radiation and the treatment and management of radiation-exposed persons can be obtained from ATSDR, your state and local health departments, and university medical centers. For clinical consultation and assistance, physicians and other health care providers are urged to contact

Radiation Emergency Assistance Center/Training Site (REAC/TS)
Telephone: (615)-576-3131 (day); (615) 481-1000 (24-hour hotline)
c/o Oak Ridge Institute for Science and Education, P.O. Box 117,
Oak Ridge, Tennessee, 37831-0117.

Information and assistance may also be obtained from the Nuclear Regulatory Commission (202) 492-7000 and CHEMTREC ([800] 424-9300, 24-hour hotline) or from the offices listed below.

The United States Department of Energy (DOE) regional coordinating offices should be notified for radiological assistance as soon as possible. At the request of a patient or the attending physician, a DOE radiologic assistance team physician may give advice regarding hospitalization and further definitive treatment. The physician may also make available special DOE medical facilities for the diagnosis and treatment of radiation injury. DOE's geographical areas of responsibility are listed below. Through this single contact, the resources of thirteen federal agencies will be made available.

Department of Energy Regional Offices

Region 1 (Connecticut, Delaware, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont)

Brookhaven Area Office
(516) 345-2200
Upton, Long Island
New York, NY 11973

Region 2 (Arkansas, Kentucky, Louisiana, Mississippi, Missouri, Puerto Rico, Tennessee, Virginia, Virgin Islands, and West Virginia)

Oak Ridge Operations Office
(615) 576-6833 or (615) 525-7885
PO Box E
Oak Ridge, TN 37831

Region 3 (Alabama, Canal Zone, Florida, Georgia, North Carolina, and South Carolina)

Savannah River Operations Office
(803) 824-6331, ext. 3333
PO Box A
Aiken, SC 29802

Region 4 (Arizona, Kansas, New Mexico, Oklahoma, and Texas)

Albuquerque Operations Office
(505) 844-4667
PO Box 5400
Albuquerque, NM 87115

Region 5 (Illinois, Indiana, Iowa, Michigan, Minnesota, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin)

Chicago Operations Office
(312) 972-5731 or (312) 972-4800
9800 S Cass Avenue
Argonne, IL 60439

Region 6 (Colorado, Idaho, Montana, Utah, and Wyoming)

Idaho Operations Office
(208) 526-1515
PO Box 2108
Idaho Falls, ID 83401

Region 7 (California, Hawaii, and Nevada)

San Francisco Operations Office
(510) 273-4237
333 Broadway
Oakland, CA 94612

Region 8 (Alaska, Oregon, and Washington)

Richland Operations Office
(509) 842-7381
PO Box 550
Richland, WA 99352

Answers to Pretest and Challenge Questions

Pretest questions are on page 1. Challenge questions begin on page 5.

Pretest

(a) Consultation for treatment of persons exposed to radiation may be obtained from REAC/TS at (615) 576-3131 (day) or (615) 481-1000 (24-hour hotline) or from other sources listed on page 29.

(b) Ideally, decontamination should be performed immediately at the site of the accident. Attending personnel must be properly protected to prevent secondary contamination. After emergency care for life-threatening trauma has been administered, the patients' contaminated clothing should be removed and double-bagged. The patients' skin and hair should be flushed with water, and the contaminated water should be caught in a child's play pool or other device for later disposal. A mild soap may be used to remove oily or adherent material. Monitoring the clean, dried skin with a beta-gamma counter between flushings will indicate the effectiveness of the decontamination procedure.

If the accident occurs in inclement weather or at a site where washing facilities are unavailable or if the patient is in need of immediate medical care, decontamination may have to be delayed. In that case, care must be taken to prevent the spread of contamination during transport by wrapping the patient in blankets. If the hospital or other medical facility is not prepared to handle a patient who is externally contaminated with radioactivity, a temporary decontamination station can be set up at the medical care facility. It should be located outside, but if that is not feasible, it should be far removed from normal activity and other patient care areas. If decontamination is performed indoors, ventilation should be suspended so that no radioactivity escapes the room. Butcher paper taped to the floor and other surfaces is an effective barrier. All potentially contaminated material, including debrided tissue, must be collected in plastic bags for proper disposal. Attending personnel must be properly attired with disposable jumpsuits, gloves, or other protective equipment to avoid contamination through contact.

(c) The potential health consequences will depend on the boy's interaction with the radioactive material. For example, it is not known whether the boy contacted the material and subsequently ingested radioactive material through hand-to-mouth activity, which would result in an internal contamination hazard. An external radiation hazard could exist if the boy contacted the material and is carrying radionuclides on his skin. Finally, the boy may have only approached the source, but may have been close enough to be exposed to beta and gamma radiation.

Assuming no contact occurred and the boy's proximity to the source were known, a radioactivity counter could provide dosimetric information that would aid in estimating his exposure. Maximum potential dose can also be calculated based on the characteristics of the source and the presumed location of the boy. The intensity of radiation decreases as the distance from the source increases, in accordance with the "inverse square" rule.

It is unlikely that the occupants of the houseboat would be affected by beta radiation, which has a relatively short range and can usually be stopped by a few feet of air. Gamma radiation has greater penetration than beta radiation; therefore, gamma radiation could have reached the houseboat about 20 yards from the source. However, shielding by the houseboat or other structures could reduce the radiation. A gamma counter might be used to obtain direct dosimetric information inside the houseboat.

(d) In this case, it is unlikely that any steps will be required to protect the members of the community who rely on the river for drinking water; however, a public health official will make that determination. Iodide-131 has a radiation half-life of 8 days. In just 32 days (4 half-lives) the amount of radioactivity will be one-sixteenth of what it was originally. Dilution by the river will also reduce the concentration of radioactivity.

Should the radioactivity level be of concern, an alternate source of water can be supplied to the community during the time required for the radioactive material to decay to a level that is considered to be safe by a health physicist. The antidote for radioactive iodide is early administration (within about 2 hours of ingestion of radioactive iodine) of SSKI (supersaturated potassium iodide [KI] solution) or iodide tablets. Stable iodide blocks absorption of iodide-131 in the thyroid. Oral administration of stable iodide is an effective and relatively inexpensive means to protect exposed residents of a community.

Cesium-137 has a 30-year radiologic half-life. It would take 120 years for the radioactivity from this source to decay to one-sixteenth of its original value. The water could remain unusable for a prolonged period depending on the concentration of cesium-137 and the characteristics of the river (e.g., volume and flow rate).

Cesium is distributed uniformly throughout the body and is rapidly eliminated by the kidneys. The experimental antidote for cesium is oral administration of ferric cyanoferrate (II). Commonly referred to as Prussian blue, this antidote binds the cesium ions that are enterically cycled and prevents their reabsorption from the gastrointestinal tract. The effectiveness of the antidote depends on the length of treatment and how soon after exposure it is started. However, Prussian blue is not approved by the Food and Drug Administration for general use or as an antidote for radioactive cesium. A radiation specialist at REAC/TS should be consulted before the antidote is administered.

Challenge

(1) The RWF for beta or gamma radiation is one; therefore, a dose of 50 mrads of beta or gamma radiation is equivalent to 50 mrem or 0.05 rem. One Sievert equals 100 rem; therefore, 0.05 rem equals 0.0005 (5×10^{-4}) Sv.

(2) The RWF for X radiation is also one; therefore, a dose of 50 mrads of X radiation would produce the same biologic effect as 50 mrads of gamma or beta radiation.

Iodide-131 is not an alpha-emitter; however, if the radioactive material was emitting alpha particles and the material was ingested, the biologic effectiveness would be greater. The RWF for alpha particles is 20, which indicates a given dose of alpha radiation is twenty times more biologically effective than the same dose of beta or gamma radiation.

(3) Potential sources of radiation for the truck driver, as well as the general public, are as follows:

- Cosmic radiation and terrestrial radiation each produce an average dose rate of 30 mrem/year. Radon exposure provides an additional dose of about 200 mrem/year.
- Potassium-40 naturally present in human tissue contributes an average dose rate of about 65 mrem/year.
- Building and construction materials contribute variable dose rates. Occupants of wood frame buildings typically receive less than 10 mrem/year; occupants of masonry structures receive about 13 mrem/year.
- Atmospheric fallout provides an exposure dose rate of about 5 mrem/year.
- Consumer products, including tobacco, contribute a dose rate of less than 5 mrem/year when expressed as whole-body exposure.
- Medical diagnostic and therapeutic radiation is variable and generally applied locally; the average dose rate due to medical procedures is estimated to be 100 mrem/year.

(4) It is not likely that the radioactivity is the direct cause of the chest pain. If the iodide-131 vaporized and was inhaled, it would be absorbed from the lungs into the bloodstream and concentrated in the thyroid. However, this action would cause the patient no immediate discomfort. The cause of the chest pain must be sought elsewhere.

(5) If the boy had no physical contact with the radioactive material and was only irradiated by the gamma and beta energy, he is not a radiation hazard to others. Had the boy contacted the waste and radioactive material was transferred to his skin or clothing, then he would be a hazard because the residue would continue to emit radiation and irradiate those nearby, or he could secondarily contaminate others through contact.

(6) All three of these persons are at increased risk of cancer, and the risk increases in proportion to the dose of radiation received. If the boy did not contact the radioactive material, he presumably received less radiation than the driver and his assistant, and therefore, would be at much less risk. A small proportion of persons exposed to radiation will develop cancer as a result; if exposed persons do develop cancer, it may never be certain whether the cancer was the result of radiation exposure or other causes. (A carcinoma induced by radiation is histologically indistinguishable from other carcinomas).

(7) Acute radiation syndrome is characterized by nausea and vomiting, which begins within 1 to 4 hours after exposure and may last as long as 48 hours, with the extent of symptoms related to the severity of exposure. The onset of vomiting for these patients is delayed, occurring about 36 hours after exposure; therefore, it is unlikely that these symptoms are directly due to radiation exposure. The cause must be sought elsewhere (e.g., anxiety). If the onset of nausea and vomiting was as late as 4 hours after exposure, the hematopoietic subsyndrome would likely ensue, and illness due to bleeding and infection could develop. In either case, with appropriate supportive care, the driver and his assistant should recover.

(8) Pertinent clinical history includes proximity to the source and duration of the exposure. Whether gastrointestinal symptoms (nausea, vomiting, and diarrhea) have occurred is important because the time of onset of these symptoms can be inversely correlated with the severity of exposure. A complete blood count, including a lymphocyte count, can also help to estimate the severity of exposure; these tests should be repeated several times during the first few days after exposure.

(9) A useful and sensitive biomarker for radiation exposure in general is the chromosome aberration assay. Radiation induces several characteristic but nonspecific chromosomal abnormalities, particularly dicentric chromosomes, in peripheral blood lymphocytes. The optimum time to perform the assay is within hours to a few weeks after exposure. Only a few laboratories are prepared to perform and interpret this radiation cytogenetic assay; call REAC/TS at (615)-576-3131 (day) or (615) 481-1000 (24-hour hotline) for further information.

(10) Assuming the truck driver and his assistant experienced no internal contamination, treatment is supportive and symptomatic. See page 24 for a treatment scheme that is based on the degree of irradiation.

During the next week, the boy's lymphocyte count should be periodically checked; no other immediate follow-up is required. An ongoing medical surveillance program is unwarranted unless the clinical evidence contradicts the health physicist's original estimate of maximum radiation exposure indicated in Challenge question 1. A whole-body dose of 50 mrads is similar to doses received in some medical diagnostic procedures.

(11) Fear is a natural reaction when people feel they may have been exposed to radiation. Reassurance is needed to alleviate the emotional and psychologic stresses that are caused when an accident involving radioactivity occurs. (See Ricks et al., 1991, in *Suggested Reading List*, page 29, for a discussion of the psychologic aspects of radiation exposure.)

You could point out that the levels of radioactivity initially found in the river soon after the accident were low (i.e., 20 pCi/L). Depending on the dynamics of the river, the radioactivity level is likely to be even lower now. The proposed drinking water standard for iodine-131 is 108 pCi/L.

To further reassure these patients, you could suggest that they have their water tested for radioactivity. You or the health physicist could also calculate the potential maximum amount of radiation exposure and compare this to information in the literature (e.g., Table 6, page 17). No immediate clinical symptoms have been associated with the amount of radiation these patients were likely to have received by ingesting or contacting the contaminated water, and the additional long-term risk of cancer at these radiation levels is negligible.

ATSDR
September 1992

Case Studies in Environmental Medicine

14

Radon Toxicity

Environmental ALERT . . .

☑ ***Indoor radon exposure may result in 7,000-30,000 lung cancer deaths annually in the United States.***

☑ ***Radon may be second only to smoking as a cause of lung cancer.***

☑ ***The combination of smoking and radon exposure results in an especially serious health risk.***

☑ ***The risk of lung cancer due to indoor radon exposure can be decreased with current technology.***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. See pages 21 to 23 for further information about continuing medical education credits and continuing education units.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

Chronic cough and weight loss in a nonsmoking 56-year-old woman

A 56-year-old housewife seen at your office has a 3-month history of chronic, nonproductive cough, which has recently become unresponsive to over-the-counter liquid cough suppressants. She denies having shortness of breath, wheezing, chest pain, hemoptysis, fever, chills, sore throat, hoarseness, or postnasal drip. Her cough is independent of time of day, physical activity, weather conditions, and exposure to dust or household cleaning agents. Furthermore, her daughter's cigarette smoke does not seem to aggravate the cough. She notes that she has been feeling fatigued and, without dieting, has lost 18 pounds over the past 6 months.

Her past medical history is noncontributory. She is a nonsmoker and nondrinker and does not come in contact with any known chemical substances or irritants other than typical household cleaning agents. Her father died at age 65 of a myocardial infarction, and her mother had breast cancer at age 71. Her first husband died of a cerebrovascular accident 3 years ago. Newly remarried to a retired shipyard worker, she and her current husband live with her 28-year-old daughter and 9-year-old grandson in their New Hampshire home. She has not been outside the New England area for the last 5 years.

Results of the physical examination, including HEENT and chest examination, were normal. There is no cyanosis or clubbing of the extremities, and there are no palpable lymph nodes. Blood tests, including a complete blood count and chemistry panel, are normal, with the exception of a total serum calcium level of 12.7 mg/dL (normal range: 9.2 to 11.0 mg/dL). However, a chest radiograph reveals a noncalcified, noncavitary 3.5-cm mass located within the parenchyma adjacent to the right hilum. There are no other radiographic abnormalities. Results of a PPD skin test for tuberculosis are negative. Urinalysis results are normal.

Pretest

(a) What is the differential diagnosis for this woman's condition?

(b) What further testing might you order?

(c) List several environmental causes that have been associated with this patient's probable disorder.

(d) What treatment options might you consider?

Answers can be found on page 18.

Exposure Pathways

Sources of Radon Exposure

- ☐ **Radon, a colorless, odorless gas, is both chemically inert and imperceptible; it decays into a series of progeny, some of which are short-lived and emit bursts of harmful alpha particles.**
- ☐ **Soil is the main source of indoor radon; however, building materials and water supply can also be sources.**

Radon gas is derived from the radioactive decay of radium, a ubiquitous element found in rock and soil. The decay series begins with uranium-238 and goes through four intermediates to form radium-226, which has a half-life of 1600 years. Radium-226 then decays to form radon-222 gas. Radon's half-life, 3.8 days, provides sufficient time for it to diffuse through soil and into homes, where further disintegration produces the more chemically and radiologically active radon progeny ("radon daughters"). These radon progeny, which include four isotopes with half-lives of less than 30 minutes, are the major source of human exposure to alpha radiation (high-energy, high-mass particles, each consisting of two protons and two neutrons). This alpha radiation is responsible for cellular transformation in the respiratory tract, which results in radon-induced lung cancer.

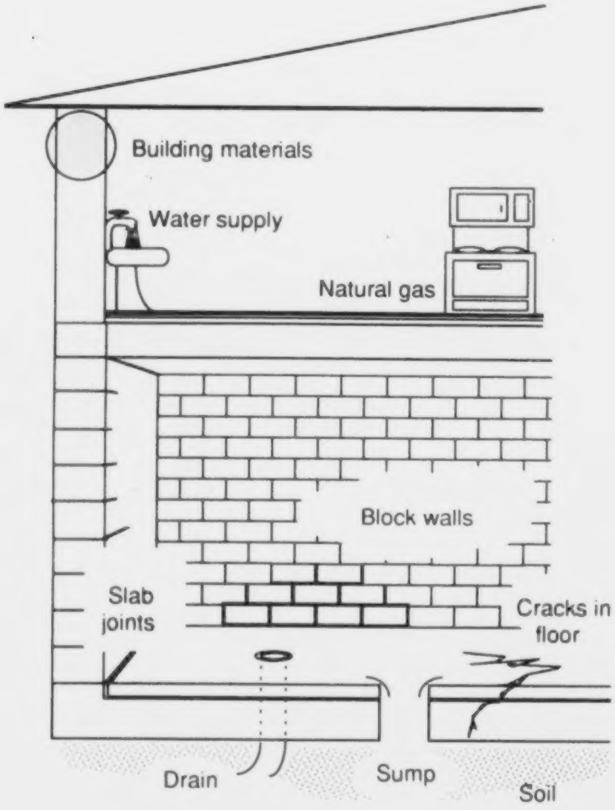
Radon itself is imperceptible by odor, taste, and color, and causes no symptoms of irritation or discomfort. There are no early signs of exposure. Only by measuring actual radon levels can persons know whether they are being exposed to excessive levels of radon gas. Radon seeps from the soil into buildings primarily through sump holes, dirt floors, floor drains, cinder-block walls, and through cracks in foundations and concrete floors (Figure 1). When trapped indoors, radon can become concentrated to dangerous levels. When radon escapes from the soil to the outdoor air, it is diluted to levels that offer relatively little health risk.

Radon gas can enter a building by diffusion, but pressure-driven flow is a more important mechanism. Negative pressure in the home relative to the soil is caused by exhaust fans (kitchen and bathroom), and by rising warm air created by fireplaces, clothes dryers, and furnaces. In addition to pressure differences, the type of building foundation can affect radon entry. Basements allow more opportunity for soil gas entry, but slab-on-grade foundations (no basement) allow for less. In most cases, the slight increase of indoor radon due to home "tightening" for energy conservation is small in comparison with the amount of radon coming from the soil.

- ☐ **Although slab-on-grade foundations allow for less soil gas entry than do basements, both types of foundations could permit entry of radon.**

Normally, construction materials do not contribute significantly to indoor radon levels. In rare cases, however, building materials themselves have been the main source of radioactive gas. Building materials contaminated with vanadium mill tailings in Monticello, Utah, and uranium mill tailings in Grand Junction, Colorado, were an important source of radon. (Tailings consist of the sand-like material remaining after minerals are removed from ore.) Also, concrete made from phosphate slag in Idaho and Montana and insulation from radium-containing phosphate waste from the state of Washington have been found to emit high levels of radon.

Figure 1. Sources of radon and common entry points


Building materials
Water supply
Natural gas
Block walls
Slab joints
Cracks in floor
Drain
Sump
Soil

Radon may be carried into some homes via the water supply. With municipal water or surface reservoirs, most of the radon volatilizes to air or decays before the water reaches homes. However, water from private wells may be another matter. Groundwater that comes from deep subterranean sources and passes over rock rich in radium, such as that found in northern New England, may dissolve some of the radon gas produced from radium decay. As the water splashes during showering, toilet flushing, dishwashing, and laundering, radon is released into the air and may result in inhalation exposure. Radon may also be present in natural gas supplies.

Challenge

(1) Additional information for the case study: Your local newspaper recently featured an article on radon and urged that all homes in your community be tested. Your patient tests her home and finds the living space averages 35 picocuries per liter (pCi/L). Discuss how construction of the patient's house can affect this level.

Hazard Assessment

Respiratory Dose and Units of Measure

☐ **Radon can be detected only by testing.**

Since the health effects of radon are insidious and have a long latency period, it is important to measure exposure to the gas empirically. Techniques for measuring radon are discussed below, in the subsection entitled Radon Detection (p. 11). Included here is a review of the basic unit of radon measurement and the factors that affect the risk associated with radon exposure.

The relationship between exposure to radon and the dose of decay products that reaches target cells in the respiratory tract is complex. Some factors that influence the pulmonary radiation dose include the following:

☐ **EPA recommends remediation for homes with radon levels at or above 4 pCi/L.**

characteristics of the inhaled air — free or unattached radon progeny deposit more efficiently than progeny attached to dust or other particles; of the attached progeny, only those adhering to the smallest particles are likely to reach the bronchi

amount of air inhaled — the amount and deposition of inhaled radon decay products vary with the flow rate in each airway segment

breathing pattern — the proportion of oral to nasal breathing will affect the number of particles reaching the airways

architecture of the lungs — sizes and branching pattern of the airways affect deposition; these patterns may differ between children and adults, and between males and females

biologic characteristics of the lungs — the dose increases as the mucociliary clearance slows and diminishes with increasing thickness of the mucous layer

It is possible, therefore, that two environments with the same radon measurement (e.g., a dusty mine and a home environment) may deliver different doses of alpha radiation to a person's lungs. Likewise, two persons in the same environment may receive differing doses of alpha radiation to the target cells of their lungs because of differing breathing patterns and pulmonary architecture.

The concentration of various progeny is ultimately related to lung injury and thus might be the most appropriate measure of respiratory exposure. On the basis of both animal and human data, it can be assumed, however, that the higher the radon level a person experiences, the more likely it is that the person will develop lung cancer. For convenience, indoor air measurements, therefore, usually measure radon gas itself. These measurements are expressed in picocuries per liter (pCi/L) of air, where a picocurie is equivalent to 0.037 disintegrations per second. The U.S. Environmental Protection Agency (EPA) has recommended that remedial action be taken to lower the amount of radon in homes if the measured level is 4 pCi/L or greater.

Risk Estimates

Even conservative estimates based on current knowledge suggest that radon is one of the most important environmental causes of death. EPA estimates that approximately 14,000 deaths annually in the United States are due to lung cancer caused by indoor radon exposure. It has also been estimated that approximately 14% of all current cases of lung cancer are attributable to radon.

For a lifetime exposure to radon at 4 pCi/L, EPA estimates that the risk of developing lung cancer is 1% to 5%. The National Research Council estimates the risk at 0.8% to 1.4%.

- ☐ **For a lifetime exposure at EPA's recommended guideline of 4 pCi/L, EPA estimates that the risk of developing lung cancer is 1% to 5%, depending on whether a person is a smoker, former smoker, or nonsmoker.**

Many factors influence the risk of lung cancer due to radon exposure; among these are age, duration of exposure, time since initiation of exposure, and cigarette smoking (Figure 2). In assessing the risk of radon in a home, one must consider not only the level of radon, but also the occupants and their lifestyles. Are there any smokers? Any children? How much time is spent in the home? Where do occupants sleep? The highest radon levels are typically found in the lowest level of the house. If well water is the major source of radon, upper floors can be affected more than lower floors. In colder climates, radon levels are often higher in the winter and lower in the summer.

- ☐ **The overall risk of radon exposure is related not only to its level in the home, but also to the occupants and their lifestyles.**

Figure 2. Radon risk evaluation chart

RADON RISK IF YOU SMOKE

Radon Level	*If 1000 people who smoked were exposed to this level over a lifetime. . .*	*The risk of cancer from radon exposure compares to. . .*	*What To Do: Stop Smoking and. . .*
20 pCi/L	About 135 people could get lung cancer	← 100 times the risk of drowning	Fix your home
10 pCi/L	About 71 people could get lung cancer	← 100 times the risk of dying in a home fire	Fix your home
8 pCi/L	About 57 people could get lung cancer		Fix your home
4 pCi/L	About 29 people could get lung cancer	← 100 times the risk of dying in an airplane crash	Fix your home
2 pCi/L	About 15 people could get lung cancer	← 2 times the risk of dying in a car crash	Consider fixing between 2 and 4 pCi/L
1.3 pCi/L	About 9 people could get lung cancer	(Average indoor radon level)	(Reducing radon levels below 2 pCi/L is difficult)
0.4 pCi/L	About 3 people could get lung cancer	(Average outdoor radon level)	

Note If you are a former smoker, your risk may be lower

RADON RISK IF YOU'VE NEVER SMOKED

Radon Level	*If 1000 people who never smoked were exposed to this level over a lifetime. . .*	*The risk of cancer from radon exposure compares to. . .*	*What To Do:*
20 pCi/L	About 8 people could get lung cancer	← The risk of being killed in a violent crime	Fix your home
10 pCi/L	About 4 people could get lung cancer		Fix your home
8 pCi/L	About 3 people could get lung cancer	← 10 times the risk of dying in an airplane crash	Fix your home
4 pCi/L	About 2 people could get lung cancer	← The risk of drowning	Fix your home
2 pCi/L	About 1 person could get lung cancer	← The risk of dying in a home fire	Consider fixing between 2 and 4 pCi/L
1.3 pCi/L	Less than 1 person could get lung cancer	(Average indoor radon level)	(Reducing radon levels below 2 pCi/L is difficult)
0.4 pCi/L	Less than 1 person could get lung cancer	(Average outdoor radon level)	

Note If you are a former smoker, your risk may be higher

Who's at Risk

As early as the 16th century, Paracelsus and Agricola described a wasting disease of miners. In 1879, this condition was identified as lung cancer by Herting and Hesse in their investigation of miners from Schneeberg, Germany. Radon itself was discovered some 20 years later by Rutherford. Subsequently, an increase in the incidence of lung cancer among miners was linked to radon exposure in mines. Underground uranium mines found throughout the world, including the western United States and Canada, pose the greatest risk because of their high concentration of radon. Iron ore, potash, tin, fluorspar, gold, zinc, and lead mines also have been found to have significant levels of radon, often due to radium in the surrounding rock. In the past, it was not uncommon to use the tailings from these mines as fill on which to build homes, schools, and other structures.

Indoor radon has been widely recognized as a potential problem in Europe and the Scandinavian countries since the 1970s. Public awareness in the United States was heightened in December 1984, when Stanley Watras, a worker at the Limerick nuclear plant in Pennsylvania, began setting off radiation alarms when he entered the plant. The cause was traced to excessive radon levels in his home, which were found to be 500 times the level at which EPA currently recommends remediation (4 pCi/L).

In 1987, the federal government allotted $10 million to the states to determine the extent of radon contamination in homes and schools and subsequently amended the Toxic Substances Control Act to assist the states "in responding to the threat to human health posed by exposure to radon." In 1988, EPA and the Office of the Surgeon General jointly recommended that all U.S. homes below the third floor be tested for radon. In 1990, Congress appropriated $8.7 million for grants to states to develop and enhance programs to reduce radon risk in homes and schools. It has become standard practice in some states to measure radon levels in homes at the time of real estate transactions.

The amount of radon emanating from the earth and concentrating inside homes varies considerably by region and locality. Nearly every state in the United States has dwellings with measured radon levels above acceptable limits. EPA estimates that 6% of American homes (approximately 6 million) have concentrations of radon above 4 pCi/L. In Clinton, New Jersey, near a geologic formation high in radium called the Reading Prong, all 105 homes tested were above the recommended guidelines, 40 had levels exceeding 200 pCi/L. In the Stanley Watras home, levels of 2700 pCi/L were found in the basement.

☐ **Miners in uranium and other types of underground mines may have increased radon exposure.**

☐ **Approximately 6 million homes in the United States have radon levels above 4 pCi/L.**

☐ **Exposure to excessive radon levels increases the already elevated risk of lung cancer for smokers.**

Areas of the country that are likely to have homes with elevated radon levels are those with significant deposits of granite, uranium, shale, and phosphate — all high in radium content and, therefore, potential sources of radon gas. Some homes in these areas, however, may not have elevated levels of radon. Due to the many determinants of indoor radon levels, local geology alone is an inadequate predictor of risk.

Currently, the only way to determine indoor radon concentration is by testing. A home located 100 feet away from the Watras' home did not have measured radon concentrations that required remediation, yet both houses are located on the same geologic formation. Other factors found to predispose homes to elevated levels of radon include soil porosity, foundation type, location, building materials used, entry points for soil gas, building ventilation rates, and source of water supply. Further research is being conducted on ways to predict which homes are most likely to have significant levels of radon.

Several studies have shown that smokers exposed to radon are at greater risk for lung cancer than nonsmokers similarly exposed. It is generally believed that exposure to radon and cigarette smoking are synergistic; that is, the combined effect exceeds the sum of their independent effects. The risk of lung cancer from radon exposure is estimated to be 10 to 20 times greater for persons who smoke cigarettes in comparison with those who have never smoked. According to the EPA Office of Radiation Programs, a breakdown of the contribution of smoking and radon exposure to lung cancer deaths in the United States illustrates that of every 100 persons who have died of lung cancer, approximately 70 were current smokers, 24 were former smokers, and 6 had never smoked. It is estimated that radon contributed to 20% of the deaths in each category.

Data on the effects of radiation in children are limited, and even less is known about the effects of radon exposure in this age group. Cancer development in Japanese atomic bomb survivors suggests an increased susceptibility to radiation in children compared with that in adults. Children also have different lung architecture, resulting in a somewhat more concentrated dose of radiation to the respiratory tract, and children have a longer latency period ahead of them in which to develop cancer. However, there are currently no conclusive data on whether children are at greater risk than adults from radon.

Challenge

(2) Who else in the home of the patient discussed in the case study could be at risk for lung cancer as a result of elevated radon levels?

(3) Would your patient's neighbors be equally at risk of exposure to radon? Explain.

(4) How are the risks of radon exposure increased for your patient's daughter, who is a smoker? How does the daughter's smoking affect the risk for other members of the family?

Physiologic Effects

Radon exposure causes no acute or subacute health effects, no irritating effects, and has no warning signs at levels normally encountered in the environment. The only established human health effect currently associated with residential radon exposure is lung cancer. Epidemiologic studies of miner cohorts have reported an increased frequency of chronic, nonmalignant lung diseases such as emphysema, pulmonary fibrosis, and chronic interstitial pneumonia, all of which increased with increasing cumulative exposure to radiation and with cigarette smoking.

Epidemiologic studies and a recent study of groundwater radon and cancer mortality have found no association with extrapulmonary cancers, such as leukemias and gastrointestinal cancers. There is also no evidence that environmental radon exposure is causally associated with adverse reproductive effects.

- ☐ **The primary adverse health effect of exposure to radon is lung cancer.**
- ☐ **The synergistic mechanism(s) of cigarette smoking and radon exposure are not known, although the adverse health effects of the combination are clear.**

☐ **Radon progeny can be inhaled either as free particles or attached to dust. Free progeny preferentially deposit in the bronchi, the site of most lung cancers.**

Due to their charged state and solid nature, radon progeny rapidly attach to most surfaces they encounter, including walls, floors, and airborne particulates. They can be inhaled, therefore, either as free, unattached particles or attached to airborne dust. The smaller dust particles can deposit the radon progeny deep in the lungs. Being ionized, the progeny tend to attach to the respiratory epithelium. Through mucociliary action, the progeny are eventually cleared from the respiratory tract, but because of their short half-life, they can release alpha particles before being removed. The total amount of energy deposited by the progeny is approximately 500 times that produced in the initial decay of radon. When these emissions occur within the lungs, the genetic material of cells lining the airways can be damaged, resulting in lung cancer.

The risk of lung cancer due to radon exposure is thought to be second only to that of smoking. The synergism between cigarette smoking and radon places the large population of current and former smokers at particularly high risk for lung cancer. Although the net consequence of cigarette smoking and exposure to radon decay products has been clearly demonstrated in smokers, the mechanism of interaction is still unclear.

Most of the lung cancers associated with radon are bronchogenic, with all histologic types represented. However, small cell carcinoma occurs at a higher frequency among both smoking and nonsmoking populations of underground miners in the initial years following exposure compared with the pattern of histologic types in the general population. Other types of lung cancers seen in radon-exposed miners are squamous cell carcinoma, adenocarcinoma, and large cell carcinoma.

Challenge

(5) If the patient's daughter described in the case study were pregnant, would the fetus be at risk from maternal exposure to airborne radon?

(6) The patient's husband developed mesothelioma as a result of asbestos exposure when he worked in the shipyards. What might have been the role of radon in the development of this condition?

Treatment and Management

Currently, no effective communitywide screening methods are available for medical prevention or early diagnosis and treatment of lung cancer (radon-induced or otherwise). Routine chest radiographs and sputum cytology are ineffective for lung cancer screening associated with cigarette smoking and would presumably be ineffective for lung cancer associated with radon as well. The most effective methods of prevention are reduction of radon exposure and modification of other simultaneous risk factors for lung cancer, such as smoking. Smoking cessation coupled with detection and mitigation of high radon levels is currently the only long-term solution for reducing the risk of lung cancer.

☐ **Generally, the most effective methods to reduce the risk of lung cancer are smoking cessation and radon mitigation.**

☐ **The risk of cancer due to radon is often underestimated by the public; this bias may discourage assessment and abatement measures in the home.**

Several studies have noted optimistic biases in the public's assessment of the risk due to radon. A New Jersey study found that this bias may discourage testing and subsequent implementation of control measures. In Maine, homeowners were found to greatly underestimate the risk, and abatement behavior was not significantly related to the actual risk.

Primary care physicians and public health professionals should promote public awareness so that the radon problem is seen in the proper perspective, leading to appropriate mitigation action when indicated. Physicians and public health officials should therefore test their own homes to relate their experience to others and to provide guidance on how to carry out the testing.

Radon Detection

Radon levels cannot be accurately predicted solely on the basis of factors such as location, geology, home construction, and ventilation. A recent survey of Connecticut homes indicates that the age of the house and the presence of a cinder-block foundation have a statistically significant, positive correlation with radon levels. Measurement is the key to identifying the problem. Radon detection kits are available in most hardware stores.

☐ **Radon levels cannot be predicted; they must be measured.**

Short-term testing (lasting a few days to several months) is the quickest way to determine if a potential problem exists. Charcoal canisters, charcoal liquid scintillation detectors, electret ion detectors, alpha-track detectors, and continuous monitors are currently the most common short-term testing devices. Short-term testing should be conducted in the lowest inhabited area of the home, with the doors and windows shut.

☐ **The most common methods of radon measurement are charcoal canisters, charcoal liquid scintillation detectors, electret ion detectors, alpha-track detectors, and continuous monitors.**

Long-term testing (lasting up to 1 year) will give a better reading of a home's year-round average radon level than will a short-term test. Alpha-track detectors and electret ion detectors are the most common long-term testing devices. Exposed devices are sent via mail to a certified laboratory for analysis. These devices measure radon gas levels, rather than radon progeny; thus, the units reported are in picocuries of radon per liter of air (pCi/L).

The charcoal canister is a small can containing charcoal and a filter to keep out radon progeny. It is inexpensive ($10 to $25) and is generally used for short-term testing (3 to 7 days). The alpha-track device contains a small piece of plastic in a filtered container. As the radon gas that has entered the container decays, the alpha particles form etch tracks. These tracks can be counted using a special technique. The cost of the alpha-track device is roughly twice that of the charcoal canister, and it may be used to measure cumulative exposure over a longer period (several weeks to a year).

Radon Abatement

☐ **The cost of remediation to reduce radon levels in the average home is about $1200.**

☐ **Available procedures to lower indoor radon levels are, dollar for dollar, very effective in saving lives.**

☐ **Subslab depressurization is one of the most effective methods of lowering radon levels in many homes.**

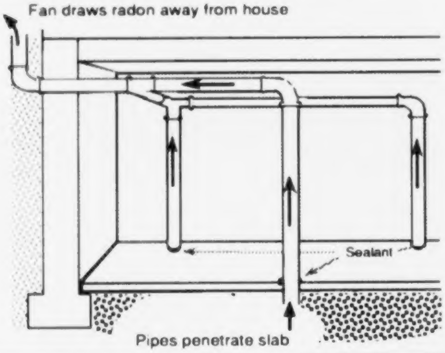
How cost-effective is radon mitigation compared to other investments in health protection? The Swedish government plans to spend approximately $1000 per home reducing high radon levels, resulting in about $10,000 of cost per life spared. EPA estimates that the cost of remediation in most homes is less than $1500. The cost of radon testing and mitigation per life saved compares favorably with that of other government programs.

If excessive levels of indoor radon are found in a structure, low-cost, quick-fix methods should be implemented first. These include limiting the amount of time spent in contaminated areas and increasing ventilation. It is wise to consult with the state radiation protection office before implementing major abatement projects. Methods of reduction can be obtained from several sources listed in the Suggested Reading List and in the Sources of Information section.

Besides increasing ventilation, radon control measures include sealing the foundation, subslab depressurization (creating negative pressure in the soil), pressurizing the home, and using air-cleaning devices. Methods of increasing ventilation include opening windows, ventilating basements and crawl spaces, ventilating sumpholes and floor drains to the outside of the house, and increasing air movement with ceiling fans. Ventilation must be modified properly, however, since increased ventilation can depressurize the house in some cases, causing an increase of soil gas entry to the home. Heat exchangers provide a way of bringing fresh air indoors without major heat loss, but these must be properly balanced or they can make the problem worse.

Preventing soil gas entry is more important than increasing whole-house ventilation. The former involves sealing the foundation and depressurizing the soil. Using vapor barriers around the foundation, sealing cracks and holes with epoxies and caulks, and sealing the crawl space from the rest of the house are all methods with some application. Subslab depressurization can reduce radon levels by as much as 99%. Suction puts the soil at a lower pressure than the inside of the home, preventing inward migration of soil gas. It involves sinking ventilation pipes below the foundation and continuously pumping out air (Figure 3). The cost to install subslab depressurization in an existing home is approximately $1000 to $2500 and about $100 annually for utility costs. The state radon office can be consulted to obtain a listing of radon mitigation contractors that have passed EPA's Radon Contractor Proficiency (RCP) program (see page 17). If the equipment is installed during construction of the home, however, the cost of subslab depressurization is considerably less; it is much easier to install pipes during construction than to retrofit later. Physicians and other health professionals can perform a public service by becoming acquainted with local building codes and urging local jurisdictions to include the installation of capped pipes terminating in a space under the foundation to allow for later subslab depressurization if it is needed.

Figure 3. Subslab depressurization



Challenge

(7) Where in your patient's home should detectors be placed for radon screening?

(8) What can you as a health professional do to decrease the risk of lung cancer among your patients?

Standards and Regulations

- ☐ **Currently, there are no enforceable regulations to control indoor radon levels, only guidelines and a national goal.**
- ☐ **The national goal is for indoor radon levels to be as low as those outdoors. About 0.4 pCi/L of radon is normally found in outside air.**

Currently, no regulations mandate specific radon levels for indoor residential and school environments. There are only guidelines for remediation, such as the EPA recommendations and a national goal. EPA based its guidelines not only on risk considerations, but also on technical feasibility. There is thought to be no level at which the risk of exposure to alpha emitters is zero. An EPA drinking water standard is being developed. Many standards and guidelines for radon are currently being reviewed (Table 1), and changes may occur over time. EPA or state health departments should therefore be consulted for the most up-to-date standards.

Table 1. Standards and regulations for radon

Source[*]	Focus	Level	Comments
Indoor Radon Abatement Act	Indoor air (residential)	Indoor = outdoor (≈ 0.4 pCi/L)	National goal
NCRP	Indoor air (residential)	8 pCi/L	Guideline
EPA	Indoor air (residential)	4 pCi/L	Current action level
EPA	Schools	4 pCi/L[†]	Guideline for action
EPA	Water	Under development	Proposal due 1993
NIOSH	Occupational (mining)	1 WLM[§] /yr and ALARA[¶]	Advisory; exposure limit
OSHA	Occupational	4 WLM[§] /yr	Regulation
MSHA	Mining	4 WLM[§] /yr	Regulation

[*] NCRP = National Council for Radon Protection; EPA = Environmental Protection Agency NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; MSHA = Mine Safety and Health Administration

[†] EPA recommends action below 4 pCi/L in schools on a case-by-case basis

[§] WLM = Working level month; a unit of measure commonly used in occupational environments (since WLM bears a complex relationship to pCi/L, physicians with responsibility for mine workers are urged to contact NIOSH or EPA for further information

[¶] ALARA = As low as reasonably achievable

In October 1988, the Indoor Radon Abatement Act was passed. This Act states that the "national long-term goal of the United States with respect to radon levels in buildings is that the air within buildings in the United States should be as free of radon as the ambient air outside of buildings." The Act mandates that EPA update its publication, *A Citizen's Guide to Radon*, and provide a series of action levels indicating the health risk associated with these various levels. The *Guide* will also provide information on the risk to sensitive populations, testing methods, and the cost and feasibility of mitigation techniques. Currently, EPA recommends remediation for homes and other buildings with levels above 4 pCi/L, with the caveat that corrective action be taken below this level on a case-by-case basis.

Challenge

(9) Additional information for the case study: The local power company has offered free radon detection devices to all its customers. The average level of radon in the classrooms of your patient's grandson is found to be 20 pCi/L. What is the community's recourse to protect its children?

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Sources of Information

More information on the adverse effects of radon and the treatment and management of radon-exposed persons can be obtained from ATSDR, your state and local health departments, and university medical centers. Physicians and other health professionals may obtain materials from EPA for display. The federal EPA maintains an Office of Radiation Programs, 401 M Street SW, Washington, DC 20640, telephone (202) 260-9600.

Case Studies in Environmental Medicine: Radon Toxicity is one of a series. For other publications in this series, please use the order form on the back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of the Director, at (404) 639-6204.

State Radon Contacts

Congress has mandated that each state set up an office to deal with requests for assistance.

ALABAMA	(800) 582-1866
ALASKA	(800) 478-4845
ARIZONA	(602) 255-4845
ARKANSAS	(501) 661-2301
CALIFORNIA	(800) 745-7236
COLORADO	(800) 846-3986
CONNECTICUT	(203) 566-3122
DELAWARE	(800) 554-4636
DISTRICT OF COLUMBIA	(202) 727-5728
FLORIDA	(800) 543-8279
GEORGIA	(800) 745-0037
HAWAII	(808) 586-4700
IDAHO	(800) 445-8647
ILLINOIS	(800) 325-1245
INDIANA	(800) 272-9723
IOWA	(800) 383-5992
KANSAS	(913) 296-1560
KENTUCKY	(502) 564-3700
LOUISIANA	(800) 256-2494
MAINE	(800) 232-0842
MARYLAND	(800) 872-3666
MASSACHUSETTS	(413) 586-7525
MICHIGAN	(517) 335-8190
MINNESOTA	(800) 798-9050
MISSISSIPPI	(800) 626-7739
MISSOURI	(800) 669-7236
MONTANA	(406) 444-3671
NEBRASKA	(800) 334-9491
NEVADA	(702) 687-5394
NEW HAMPSHIRE	(800) 852-3345 x4674
NEW JERSEY	(800) 648-0394
NEW MEXICO	(505) 827-4300
NEW YORK	(800) 458-1158
NORTH CAROLINA	(919) 571-4141
NORTH DAKOTA	(701) 221-5188
OHIO	(800) 523-4439
OKLAHOMA	(405) 271-5221
OREGON	(503) 731-4014
PENNSYLVANIA	(800) 237-2366
PUERTO RICO	(809) 767-3563
RHODE ISLAND	(401) 277-2438
SOUTH CAROLINA	(800) 768-0362
SOUTH DAKOTA	(605) 773-3351
TENNESSEE	(800) 232-1139
TEXAS	(512) 834-6688
UTAH	(801) 538-6734
VERMONT	(800) 640-0601
VIRGINIA	(800) 468-0138
WASHINGTON	(800) 323-9727
WEST VIRGINIA	(800) 922-1255
WISCONSIN	(608) 267-4796
WYOMING	(800) 458-5847

Answers to Pretest and Challenge Questions

Pretest

The Pretest questions are on page 1.

(a) The differential diagnosis for the patient's radiographic solitary pulmonary nodule would include

primary pulmonary malignancy
metastatic malignancy
granulomatous disease (for example, tuberculosis, coccidioidomycosis, histoplasmosis, nocardiosis)
AV malformation
pulmonary hamartoma
bronchial adenoma
pulmonary abscess
pseudonodule (e.g., nipple shadow, superficial skin lesion)
sarcoidosis

The following factors increase the likelihood of her having a pulmonary malignancy: radiographic appearance of the lesion (size and lack of calcification), age, symptoms of cough and weight loss, hypercalcemia, absence of residence in or travel to an area endemic for coccidioidomycosis (southwest United States) or histoplasmosis (Ohio/Mississippi Valley), absence of fever or evidence of infectious disease, and negative PPD skin test. The latter does not rule out tuberculosis but makes it less likely.

(b) Initially, one or more of the following might be ordered:

search for previous chest radiographs for comparison
sputum studies for cytology and cultures (standard pathogens, fungus, acid-fast bacilli)
CAT scan
fiber-optic bronchoscopy with bronchial brushings and specimens for cytology and culture

Additional tests would follow, depending on results of these initial studies. If a primary lung cancer is detected, a metastatic workup (scans of the brain, liver, adrenals, and bones) may be indicated.

(c) Environmental causes of lung cancer include

arsenic
asbestos
chloromethyl ethers
chromium
ionizing radiation (alpha, beta, gamma, or X-radiation)
nickel
polynuclear aromatic hydrocarbons (PAHs)
radon
tobacco smoke

(d) The treatment issues for this patient are beyond the scope of this monograph, and treatment would not be recommended until further studies are completed. The patient should be referred to an oncologist and chest surgeon (if she is a surgical candidate) for evaluation before treatment. Depending on histologic type, local extension into adjacent anatomical structures, presence of metastases, and the general health of the patient, treatment options would include surgical excision, radiation, chemotherapy, and possibly immunotherapy.

Challenge

Challenge questions begin on page 4.

(1) In addition to building location, the factors that influence radon gas entry into a home are

type and condition of the foundation
pressure differences between the soil and the inside of the home
building materials used
air exchange rate or ventilation

(2) Anyone who spends a significant amount of time in the home would be at risk. Data are inadequate to assess individual susceptibility to radon-induced lung cancer; however, possible reasons to be additionally concerned about members of this family include that the patient's daughter is a smoker, her grandson is still a child, and her husband has a past history of shipyard work with possible asbestos exposure. The amount of time spent at home by each family member should be considered. You might be concerned about her husband because exposures to both asbestos and radon may increase his risk of lung cancer significantly. Because he is retired, he may spend more time at home indoors, thus increasing his duration of exposure to radon.

(3) No. Everyone in the community will not be exposed to the same radon level. Regional geologic differences such as granite deposits and soil structure are major determinants of indoor radon concentration; however, local variations can be great. Even assuming all homes in the community are built on the same geologic formation, the radon level in each home cannot be predicted. The only way to determine a home's radon level is to test. The construction and condition of each house and the source of water supply may vary. Even if the neighbors were exposed to the same radon levels, they would not be at equal risk of health effects. The risk of lung cancer to each occupant does not depend only on the radon level, but also on the occupants themselves and their lifestyles.

(4) The actions of radon and cigarette smoke are probably synergistic. For your patient's daughter, who is a smoker, the risk of dying from lung cancer is 10 to 20 times greater than if she did not smoke. It is presently unknown how passive exposure to cigarette smoke affects the risk of developing lung cancer in relation to radon exposure.

(5) No, it is unlikely that the fetus would be affected by airborne radon because alpha emitters act locally on the respiratory tract, and there are no firmly established systemic effects.

(6) It is unlikely that radon would play any role in the development of mesothelioma because this is a malignancy of the pleural lining, not the lung. The risk for mesothelioma among asbestos workers is also not increased by smoking.

(7) The test kit should be placed in the lowest lived-in level of the home (for example, the basement if it is frequently used, otherwise the first floor). It should be put in a room that is used regularly (like a living room, playroom, den or bedroom) but not your kitchen or bathrooom. Place the kit at least 20 inches above the floor in a location where it won't be disturbed—away from drafts, high heat, high humidity, and exterior walls.

(8) As a health professional, you can (a) motivate all smokers to quit smoking; (b) educate and act as a resource to patients regarding radon risks; (c) help families rank the risks of the many environmental pollutants they encounter; (d) refer the family to the health department, state radon office, or EPA for more information and relate to others your experiences in testing your own home; (e) encourage detection and mitigation of radon when indicated, and encourage appropriate building techniques for new construction.

(9) There are currently no enforceable regulations to control indoor radon levels; therefore, there is no legal recourse. EPA recommends mitigation if the radon level indoors is above 4 pCi/L; the national goal is to reduce indoor radon levels to outdoor levels, about 0.4 pCi/L. Clearly the school's classrooms exceed these levels. Education and persuasion of the citizenry are methods that may motivate the community to take remedial action.

RESIDENTIAL RADON EXPOSURE AND LUNG CANCER IN SWEDEN

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Abstract *Background.* Residential radon is the principal source of exposure to ionizing radiation in most countries. To determine the implications for the risk of lung cancer, we performed a nationwide case–control study in Sweden.

Methods. The study included 586 women and 774 men 35 to 74 years of age with lung cancer that was diagnosed between 1980 and 1984. For comparison, 1380 female and 1467 male controls were studied. Radon was measured in 8992 dwellings occupied by the study subjects at some time since 1947. Information on smoking habits and other risk factors for lung cancer was obtained from questionnaires.

Results. Radon levels followed a log-normal distribution, with geometric and arithmetic means of 1.6 and 2.9 pCi per liter (60.5 and 106.5 Bq per cubic meter), respectively. The risk of lung cancer increased in relation to both estimated cumulative and time-weighted exposure to radon. In comparison with time-weighted average radon concentrations up to 1.4 pCi per liter (50 Bq per cubic meter), the relative risk was 1.3 (95 percent confidence interval, 1.1 to 1.6) for average radon concentrations of 3.8 to 10.8 pCi per liter (140 to 400 Bq per cubic meter), and it was 1.8 (95 percent confidence interval, 1.1 to 2.9) at concentrations exceeding 10.8 pCi per liter. The estimates of risk were in the same range as those projected from data in miners. The interaction between radon exposure and smoking with regard to lung cancer exceeded additivity and was closer to a multiplicative effect.

Conclusions. Residential exposure to radon is an important cause of lung cancer in the general population. The risks appear consistent with earlier estimates based on data in miners. (N Engl J Med 1994;330:159-64.)

RADON-222 in dwellings is the dominant source of exposure to ionizing radiation in most countries.[1] Nationwide measurement programs suggest that the average radon concentration in Sweden is about 2.7 pCi per liter (100 Bq per cubic meter), a level that appears higher than those in many other countries. Current standards in Sweden correspond to about 3.8 pCi per liter (140 Bq per cubic meter) for new houses and 10.8 pCi per liter (400 Bq per cubic meter) for existing houses, whereas in the United States the recommended level at which action should be taken is 4 pCi per liter (148 Bq per cubic meter).[2]

Underground miners exposed to high levels of radon progeny (also known as radon daughters because they are decay products that follow radon-222 in the uranium series that begins with uranium-238)[3] have an increased risk of lung cancer.[4] Studies in laboratory animals confirm that the inhalation of radon progeny can induce lung cancer. Quantitative assessments of risks to the population based on data in miners have considered the role of differences in age, sex, cigarette smoking, the size distribution of aerosol particles, the unattached fraction of radon progeny, breathing rate, and route,[4-6] but the value for many of these indexes is uncertain, as is their influence on estimates of risk.

The risk of lung cancer posed by residential exposure to radon has been studied in epidemiologic investigations using ecologic, cohort, and case–control designs.[7-13] Positive trends were observed in some studies but not in others, and there has been no consistent pattern to the interaction between radon exposure and smoking in relation to lung cancer.

The primary aim of this study was to narrow the uncertainty in the estimation of the risk of residential exposure to radon, which necessitated a study considerably larger than any of the earlier investigations. A further aim was to assess the interactions between residential radon exposure and other factors, primarily smoking.

METHODS

Study Subjects

The study base included all subjects 35 to 74 years of age who had lived in 1 of 109 municipalities in Sweden at some time from January 1, 1980, through December 31, 1984, and who had been living in Sweden on January 1, 1947. Fifty-six of the municipalities were selected as areas where there was a high risk of radon in dwellings according to earlier measurements, geologic information, and data on the use of uranium-rich alum shale concrete as a building material. This concrete is an important source of indoor radon in Sweden and was widely used until 1975.[5] The remaining municipalities were areas where there was a low risk of radon in dwellings. Municipalities with mining activity and the large cities of Stockholm, Göteborg, and Malmö were not included.

A total of 1500 subjects 35 to 74 years of age with primary cancer of the bronchus or lung ("lung cancer," as defined in the *International Classification of Diseases, 7th Revision*, code 162.1) diagnosed from January 1, 1980, through December 31, 1984, were selected from the Swedish Cancer Registry. This included all 650 women and a random sample of 850 men that corresponded to about 40 percent of the men with lung cancer in the study base. Twelve subjects were excluded because the medical records revealed that nine did not have primary lung cancer and that three had nonepithelial tumors. After the further exclusion of 128 subjects not residing in Sweden on January 1, 1947, 586 women and 774 men remained (Table 1). Nearly half the cases of lung cancer appeared in the group 65 to 74 years of age, and the men with the disease tended to be older than the women.

Histologic confirmation of lung cancer was available for 84.2 percent of the subjects, cytologic confirmation was available for 14.6 percent, and in 1.1 percent the diagnosis was based on other

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Supported by grants from the Swedish Radiation Protection Institute, the Swedish Cancer Society, the Swedish Council for Building Research, and the Swedish Council for Planning and Coordination of Research.

Table 1. Age Distribution of the Case Subjects with Lung Cancer and the Subjects in the Two Control Groups, According to Sex.

AGE (YR)	CASE GROUP		FIRST CONTROL GROUP		SECOND CONTROL GROUP	
	WOMEN	MEN	WOMEN	MEN	WOMEN	MEN
			number of subjects (percent)			
35–44	46 (7.9)	22 (2.8)	33 (4.5)	36 (5.2)	29 (4.5)	33 (4.3)
45–54	81 (13.8)	75 (9.7)	82 (11.2)	97 (14.0)	96 (14.8)	88 (11.4)
55–64	200 (34.1)	277 (35.8)	256 (35.1)	232 (33.4)	232 (35.7)	286 (37.0)
65–74	259 (44.2)	400 (51.7)	359 (49.2)	329 (47.4)	293 (45.0)	366 (47.3)
All	586 (100.0)	774 (100.0)	730 (100.0)	694 (100.0)	650 (100.0)	773 (100.0)

evidence (e.g., autopsy findings or operation without histologic analysis). Histopathological typing of the tumors was based on the classification of the World Health Organization (WHO).[14] The reports from the pathology departments were reviewed and used to code the cancer in 1264 subjects (92.9 percent). For the remaining subjects, the coding was based on information from the Swedish Cancer Registry. This registry used a classification that was compatible with the WHO system for squamous-cell carcinomas and adenocarcinomas but did not differentiate between small-cell and large-cell carcinomas.

Two control groups representing the study base were selected from the population registers of Statistics Sweden. Each group included 1500 subjects. The first control group was frequency-matched for age (in five-year intervals) and calendar year of residence with the case group, and it originally included 775 women and 725 men. Immigrants to Sweden after January 1, 1947, were excluded, leaving 730 women and 694 men for the subsequent analyses (Table 1). The slight differences in age distribution between the case subjects and the controls resulted from the exclusion of immigrants.

The second control group was selected according to the same criteria used to select the first group, except that in addition it was frequency-matched for vital status, with use of the Swedish Cause of Death Registry. Matching for vital status was performed to reduce potential bias in obtaining information on exposure. Subjects who had died of smoking-related causes were excluded from the second control group to avoid overrepresentation of smoking.[15] On the basis of evidence from Swedish studies,[16,17] the following diagnoses were regarded as related to smoking: cancer of the mouth, esophagus, liver, pancreas, larynx, uterine cervix, or bladder; ischemic heart disease; aortic aneurysm; cirrhosis of the liver; chronic bronchitis and emphysema; gastric ulcer; death from violent causes, and intoxication. The second control group originally included 683 women and 817 men, but after the exclusion of those who did not reside in Sweden on January 1, 1947, a total of 650 women and 773 men remained.

When the study subjects were selected (on December 31, 1986), 518 women (88.4 percent) and 706 men (91.2 percent) in the case group had died. In the first control group, 55 women (7.5 percent) and 68 men (9.8 percent) had died, and in the second control group, 572 women (88.0 percent) and 707 men (91.5 percent) had died.

Information on Radon Exposure

All the study subjects or their next of kin were mailed a standardized questionnaire inquiring about the smoking habits of the subjects and their spouses and parents. The subjects' lifetime occupational history and their residential addresses since 1947 were also investigated. Questions were asked about the type of house, the building material used, the heating system, the amount of time spent at home, and the like. In the event of an incomplete questionnaire or a failure to respond, supplementary information was obtained in telephone interviews. Those collecting the data did so without knowing whether the subject under study was a case subject or a control.

Questionnaires were returned for 1118 case subjects, as well as for 1192 and 1135 subjects in the two control groups, yielding response rates of 82.2, 83.7, and 79.8 percent, respectively. In the first control group the respondents to the questionnaire were primarily the study subjects (81.7 percent), whereas in the case group and the second control group next of kin predominated (91.8 and 90.7 percent). Among next-of-kin respondents, spouses were the most common (47.8 percent in the case group and 43.8 percent in the second control group), followed by children (39.0 and 37.9 percent in the case group and the second control group, respectively).

The assessment of each subject's exposure to radon was based on a residential history and on radon measurements. In the compilation of the residential history, data from parish registers were supplemented with information from the questionnaires, so that a complete record of residential addresses from 1947 on was made available. The radon measurements were intended to include all dwellings in which the subject had lived during a "residential period," defined as a period of two years or more from 1947 to three years before the end of follow-up. The year of diagnosis constituted the end of follow-up for the case subjects, whereas the frequency-matched year of selection was used for the controls.

A total of 13,392 residential periods were identified (Table 2), but for 7.5 percent the address could not be identified because the subject resided in an unknown place, abroad, in a hospital, on a ship, or the like. Information on addresses was available for 12,394 dwellings, or an average of 3.1, 2.9, and 2.8 dwellings per subject in the case group and the first and second control groups, respectively. Radon measurements could not be made in 3402 dwellings (27.4 percent), usually because the house no longer existed or was being used only as a summer house.

Radon was measured over a period of three months during the heating season — i.e., a time between October 1 and April 30. In each dwelling one detector was placed in a bedroom and another in the living room, mostly by personnel from the local board of public health. Radon was measured by solid-state alpha track detectors processed at the Swedish Radiation Protection Institute. The system includes an alpha track detector, a holder, a chemical etching process, and an automatic readout by an image system.[18] For a measurement period of 90 days, the total error resulting from uncertainty in calibration, film sensitivity, readout, counting statistics, and background is 10 percent at radon concentrations of 1.6 pCi per liter (60 Bq per cubic meter), 7 percent at concentrations of 3.1 pCi per liter (115 Bq per cubic meter), and 5 percent at concentrations of 10 pCi per liter (370 Bq per cubic meter). The detectors were calibrated at the Radiation Protection Institute, which has taken part in international comparisons since the 1970s with good results.[19,20]

Cumulative radon exposure since 1947 was estimated for each subject by adding the products of the measured radon level and the length of time the subject lived in each residence. Time-weighted mean radon concentrations were calculated by dividing the cumulative radon exposure by the total time spent living in residences for which radon measurements were available. In some analyses of cumulative exposure to radon, missing measurements were replaced by the median radon level for all study subjects. In other analyses, these replacements were based on information about the characteristics of the residence (the building material and type of house) obtained from the questionnaire and the characteristics of the municipality (high, medium, or low risk of radon in dwellings). Information on whether the subjects slept in a room with an open window, which may have an influence on radon exposure, was used in some analyses. Cutoff points in the analyses using time-weighted mean radon concentrations were based partly on current Swedish standards.

Smoking habits were classified according to the time-weighted mean consumption of tobacco during the subject's lifetime. Daily consumption was expressed in cigarette equivalents, with one pack (50 g) of pipe tobacco a week corresponding to 7.1 cigarettes a day. Conversions were also made for cigarillos and cigars, which were rarely used. Subjects who stopped smoking two or more years before the end of the follow-up period were classified as ex-smokers.

Each job held by a study subject was classified in one of four categories based on earlier evidence of occupational risks of lung

Table 2. Assessment of Radon Levels in Dwellings Where the Study Subjects Lived for at Least Two Years during the Period Studied.*

VARIABLE	CASE SUBJECTS WITH LUNG CANCER	FIRST CONTROL GROUP	SECOND CONTROL GROUP
		number (percent)	
Residential periods	4581	4437	4374
Addresses identified	4246 (100.0)	4138 (100.0)	4010 (100.0)
Dwellings assessed	3078 (72.5)	3030 (73.2)	2884 (71.9)
Dwellings not assessed			
House nonexistent	483 (11.4)	405 (9.8)	447 (11.1)
House used only in summer	229 (5.4)	221 (5.3)	227 (5.7)
House not used as residence	86 (2.0)	71 (1.7)	106 (2.6)
Permission for assessment withheld	141 (3.3)	198 (4.8)	168 (4.2)
House not able to be located	192 (4.5)	175 (4.2)	154 (3.8)
Other	37 (0.9)	38 (0.9)	24 (0.6)

*The assessment of residential exposure to radon is explained in greater detail in the Methods section. Percentages may not total 100 because of rounding.

cancer, including data from some Swedish studies.[21-23] Subjects working for two years or more in a job assigned to either of the two highest-risk categories were considered to have a high risk, those working only in jobs assigned to the category with lowest risk were considered to have a low risk, and the remaining subjects were considered to have a medium risk.

Subjects who lived for 10 years or more in one of the three largest cities in Sweden (Stockholm, Göteborg, or Malmö) at some time between 1947 and the end of the follow-up were classified as urban dwellers. Excess risks of lung cancer have been reported in these cities after adjustment for smoking.[24]

Statistical Analysis

The data were analyzed with the Epicure package.[25] Associations between different measures of exposure to radon and the risk of lung cancer were described with maximum-likelihood estimates of relative risk and 95 percent confidence intervals based on logistic-regression analyses.[26] The indicator variables were categories of exposure to radon, age (in five-year intervals), smoking status, urbanization, and occupational exposure. Cross-classification of these variables constituted the strata in a conditional logistic regression. Analyses of trends with a continuous variable for exposure to radon were based on a linear model of relative risk,[27] in accordance with most current analyses of studies of miners.[4] The coefficient for the linear increase in relative risk was adjusted to improve the convergence of the iterative estimation procedure,[28] and the confidence intervals were based on the likelihood-ratio criterion. The interaction between smoking and radon was assessed through a geometric combination of additive and multiplicative effects.[29] The data presented combine both control groups, because the results of analyses with each group were similar.

RESULTS

The radon levels in the 8992 homes where measurements were made followed an approximately log-normal distribution, with geometric and arithmetic means of 1.6 and 2.9 pCi per liter (60.5 and 106.5 Bq per cubic meter), respectively. The cutoff points for quartiles of radon levels were 0.8, 1.5, and 3.1 pCi per liter (30, 57, and 116.5 Bq per cubic meter), and the highest measured concentration was 183 pCi per liter (6784 Bq per cubic meter). Radon measurements were available for an average period of 23.5 and 23.0 years in the case and control groups, respectively, or 72.4 and 71.1 percent of the period intended for measurement. No measurements could be made for 79 case subjects (5.8 percent) and 271 controls (9.5 percent), and these subjects were excluded from the subsequent analyses.

Table 3 shows the relative risk of lung cancer in relation to the estimated level of residential exposure to radon, according to histologic type of cancer. When all types were considered together, there was a positive trend, with an excess relative risk of 0.10 (95 percent confidence interval, 0.01 to 0.22) per 2.7 pCi per liter. The relative risks in subjects exposed to average time-weighted radon levels of 3.8 to 10.8 pCi per liter and to levels exceeding 10.8 pCi per liter were 1.3 (95 percent confidence interval, 1.1 to 1.6) and 1.8 (95 percent confidence interval, 1.1 to 2.9), respectively. The

Table 3. Relative Risk of Lung Cancer in Sweden, 1980–1984, According to Time-Weighted Mean Residential Exposure to Radon since 1947 and Histologic Type.

HISTOLOGIC TYPE OF LUNG CANCER	RADON EXPOSURE (Bq PER CUBIC METER)*									EXCESS RELATIVE RISK PER UNIT OF RADON (95% CI)†
	≤50	>50 TO 80		>80 TO 140		>140 TO 400		>400		
	No. of Case Subjects	No. of Case Subjects	Relative Risk (CI)	No. of Case Subjects	Relative Risk (CI)	No. of Case Subjects	Relative Risk (CI)	No. of Case Subjects	Relative Risk (CI)	
All	452	268	1.1 (0.9–1.3)	272	1.0 (0.8–1.3)	246	1.3 (1.1–1.6)	43	1.8 (1.1–2.9)	0.10 (0.01–0.22)
Squamous cell	144	89	1.2 (0.9–1.7)	99	1.3 (0.9–1.8)	82	1.5 (1.1–2.1)	11	1.7 (0.8–3.7)	0.09 (0.31)‡
Small cell	110	56	0.9 (0.6–1.4)	64	1.1 (0.7–1.6)	51	1.2 (0.8–1.8)	15	2.8 (1.3–5.9)	0.15 (0.43)‡
Adenocarcinoma	121	77	1.1 (0.8–1.6)	68	1.0 (0.7–1.5)	67	1.4 (1.0–1.9)	12	2.3 (1.1–4.6)	0.17 (0.01–0.42)
Other or not determined	47	46	1.0 (0.6–1.5)	41	0.9 (0.6–1.3)	46	1.4 (0.9–2.1)	5	1.3 (0.5–3.5)	0.06 (0.34)‡

*To convert becquerels per cubic meter to picocuries per liter, divide by 37. There were 952, 561, 568, 436, and 59 controls, respectively, in the five exposure categories. Relative risks and 95 percent confidence intervals (CI) are shown after adjustment for age, occupation, sex, smoking status, and urban as compared with nonurban living.

†Values shown are per unit increase in the radon concentration (1 unit = 2.7 pCi per liter, or 100 Bq per cubic meter).

‡The trend is not statistically significant (P>0.05). Only the upper limit of the confidence interval is shown because the lower limit cannot be calculated with the method used when the confidence interval includes 0.

strongest association was suggested for small-cell carcinoma and adenocarcinoma. It should be noted that 20 tumors, which probably included mostly small-cell carcinomas, were classified as "other or not determined" because the codes in the Swedish Cancer Registry did not differentiate small-cell and large-cell carcinomas.

Interactions between estimated exposure to radon and smoking are shown in Table 4. The subjects who never smoked and were assigned to the lowest category of radon exposure were used as the reference group. In comparison, current smokers exposed to an average of more than 10.8 pCi per liter had relative risks of 25 to 30. Stronger trends in relation to radon exposure were suggested for current smokers than for subjects in the other categories of smoking habits. The interaction between residential exposure to radon and smoking exceeded an additive effect when both radon and smoking were used as continuous variables ($P = 0.02$). The combined effect appeared particularly strong in the category with the highest degree of exposure to radon.

For subjects who slept near an open window, there was no apparent trend in risk with increasing estimated radon exposure (Table 5). These subjects slept near an open window during an average of 81.6 percent of the residential period for which measurements were available. When these subjects were excluded from the analysis, the excess relative risk per 2.7 pCi of radon per liter was 0.18 (95 percent confidence interval, 0.06 to 0.37). No clear differences in the risk of lung cancer were apparent between the subjects who slept near an open window and the remaining subjects, other than differences related to radon exposure. In general, the pattern of excess risk per unit of exposure in different subcategories was similar when the subjects who slept near an open window were excluded from the analysis, but the magnitude of risk tended to be higher than that for the group as a whole (data not shown).

The trend seen in the analyses using time-weighted mean exposure was confirmed when the risk of lung cancer was related to cumulative exposure to radon and the two measures were found to be highly correlated. When the unit of exposure was defined as a combination of the average period for which exposures were estimated (32.5 years) and a radon level of 2.7 pCi per liter, the excess risk per unit of exposure was 0.11 (95 percent confidence interval, 0.01 to 0.28) when missing measurements were replaced by median levels and 0.10 (95 percent confidence interval, 0.00 to 0.36) when they were replaced by information about the house and the municipality. These values were quite similar to the risk estimated without the use of replacements for missing values (Table 3). After the exclusion of subjects who slept near an open window, the corresponding estimates of risk were 0.23 (95 percent confidence interval, 0.07 to 0.51) and 0.21 (95 percent confidence interval, 0.05 to 0.45) per unit of exposure.

DISCUSSION

Our results indicate that residential exposure to radon is an important risk factor for lung cancer in the general population. The observed excess risk of 11 percent per 2.7 pCi of radon per liter over a 32.5-year period corresponds to an excess relative risk of lung cancer of 3.4 percent per 27 pCi per liter (1000 Bq per cubic meter) per year. The exclusion of subjects who slept near an open window increased the excess risk to 22 percent per 2.7 pCi per liter over a 32.5-year period, or 6.7 percent per 27 pCi per liter per year. In miners, excess risk ranges from about 0.5 to 3 percent

Table 4. Relative Risk of Lung Cancer in Sweden, 1980–1984, According to Time-Weighted Mean Residential Radon Exposure since 1947 and Smoking Status.

SMOKING STATUS	RADON EXPOSURE (Bq PER CUBIC METER)*										EXCESS RELATIVE RISK PER UNIT OF RADON (95% CI)†
	≤50		>50 TO 80		>80 TO 140		>140 TO 400		>400		
	Subjects	Relative Risk (CI)	Subjects	Relative Risk (CI)	Subjects	Relative Risk (CI)	Subjects	Relative Risk (CI)	Subjects	Relative Risk (CI)	
Never smoked	64	1	36	1.1	35	1.0	38	1.5	5	1.2	0.07
	443	—	240	(0.7–1.7)	252	(0.6–1.5)	198	(1.0–2.3)	31	(0.4–3.1)	(0.35)‡
Exsmoker	35	2.6	21	2.4	24	3.2	27	4.5	1	1.1	0.01
	105	(1.6–4.2)	69	(1.3–4.3)	63	(1.8–5.6)	48	(2.6–8.0)	8	(0.1–9.0)	(0.66)‡
Current smoker (cigarettes/day)											
<10	103	6.2	60	6.0	62	6.1	53	7.3	12	25.1	0.16
	128	(4.2–9.2)	79	(3.8–9.4)	79	(3.9–9.5)	59	(4.5–11.7)	4	(7.7–82.4)	(0.54)‡
≥10	168	12.6	85	11.6	94	11.8	83	15.0	16	32.5	0.19
	102	(8.7–18.4)	63	(7.4–18.0)	71	(7.7–18.2)	42	(9.4–24.0)	4	(10.3–102.1)	(0.61)‡
Unknown	82	4.7	66	5.9	57	5.3	45	5.4	9	8.8	0.02
	174	(2.9–7.7)	110	(3.5–10.0)	103	(3.1–9.2)	89	(3.1–9.5)	12	(3.3–23.7)	(0.26)‡

*To convert becquerels per cubic meter to picocuries per liter, divide by 37. For each category, the number that appears on the first line under the heading Subjects is the number of case subjects and the number on the second line is the number of controls. Relative risks and 95 percent confidence intervals (CI) are shown after adjustment for age, occupation, sex, and urban as compared with nonurban living.

†Values shown are per unit increase in the radon concentration within each stratum of smoking habits (1 unit = 2.7 pCi per liter, or 100 Bq per cubic meter).

‡The trend is not statistically significant ($P \geq 0.05$). Only the upper limit of the confidence interval is shown because the lower limit cannot be calculated with the method used when the confidence interval includes 0.

Table 5. Relative Risk of Lung Cancer in Sweden, 1980–1984, According to Time-Weighted Mean Residential Radon Exposure since 1947 and the Habit of Sleeping near an Open Window.

SLEEPING NEAR OPEN WINDOW	RADON EXPOSURE (Bq PER CUBIC METER)*										EXCESS RELATIVE RISK PER UNIT OF RADON (95% CI)†
	<50		>50 TO 80		>80 TO 140		>140 TO 400		>400		
	Subjects	Relative Risk (CI)	Subjects	Relative Risk (CI)	Subjects	Relative Risk (CI)	Subjects	Relative Risk (CI)	Subjects	Relative Risk (CI)	
No or unknown	330 716	1 —	214 418	1.2 (0.9–1.5)	204 386	1.2 (1.0–1.6)	195 315	1.5 (1.1–1.9)	37 41	2.6 (1.5–4.4)	0.18 (0.06–0.37)
Yes	122 236	1.2 (0.9–1.6)	54 143	0.9 (0.6–1.8)	68 182	0.8 (0.6–1.1)	51 121	1.1 (0.7–1.7)	6 18	0.8 (0.3–2.1)	−0.03 (0.05)‡

*To convert becquerels per cubic meter to picocuries per liter, divide by 37. For each category, the number that appears on the first line under the heading Subjects is the number of case subjects, and the number on the second line is the number of controls. Relative risks and 95 percent confidence intervals (CI) are shown after adjustment for age, occupation, sex, smoking status, and urban as compared with nonurban living.

†Values shown are per unit increase in radon concentration (1 unit = 2.7 pCi per liter, or 100 Bq per cubic meter).

‡The trend is not statistically significant ($P \geq 0.05$). Only the upper limit of the confidence interval is shown because the lower limit cannot be calculated with the method used when the confidence interval includes 0.

per "working-level month,"[7] which may be converted to a range of 3 to 17 percent per 27 pCi per liter per year, assuming an equilibrium factor between the concentrations of radon progeny and radon of 0.5 and an occupancy factor of 0.8 for time spent in the home. An equilibrium factor of 0.4 may be more representative of Swedish dwellings,[3] and only about 60 percent of the time is spent in the home.[30,31] When these circumstances are taken into consideration, the excess risk in miners corresponds to 2 to 10 percent per 27 pCi per liter per year. Additional downward adjustment in the conversion of risk estimates in miners to risk estimates for residential exposures may be necessary — for example, to control for differences in breathing patterns.[6]

Assuming that we have included an exposure period appropriate for the induction of lung cancer, it seems that our risk estimates correspond well to extrapolations based on studies in miners. Three recent studies suggested risk estimates within the same range as those based on projections in miners,[8,11,13] although two other studies found no effect of radon.[10,12] All five studies were small, and there were many differences among them — for example, in relation to sex, radon levels, type of measurements, effect of smoking, and indoor air pollution, all of which are potentially important for the compatibility of the results.

The interaction between residential radon and smoking with regard to lung cancer exceeded additivity and was more consistent with a multiplicative effect. This implies that the number of radon-related lung cancers in a population depends heavily on rates of smoking and that the reverse is also true — i.e., the number of smoking-related cancers also depends on the level of radon exposure in the population. A stronger association between residential exposure to radon and lung cancer was suggested for small-cell carcinoma and adenocarcinoma than for other histologic types. In miners the picture is not fully consistent, but some studies indicate an excess risk, particularly for small-cell carcinoma.[32-34]

Bias in the selection of controls in our study was unlikely, since both control groups were population-based, the response rates were relatively high, and the results were consistent in the two control groups. Several Swedish studies show that information of high quality about a deceased subject's occupation, residential history, and history of smoking can be obtained from a next of kin with the methods used in this study.[35-37] Confounding by known risk factors for lung cancer, such as smoking, certain occupations, and urban living, was controlled for in the analysis, and no strong confounding of the association between radon exposure and lung cancer by these risk factors was indicated. If anything, the confounding was negative. It is not likely that confounding would explain relative risks on the order of 1.5 to 2, which were encountered in the highest category of exposure to radon.

There is substantial uncertainty in the estimation of exposure to radon in the study subjects, which will primarily dilute the association with lung cancer. This uncertainty depends on several factors, including errors in radon measurements, duration of measurements, number of rooms measured, occupancy, the measurement of radon instead of unattached and attached radon progeny, and measurement made recently to estimate exposure decades ago. Measurement was avoided during the summer, when many Swedes leave their homes for several weeks. It is probable that the mean radon level is about 10 percent higher during the heating season than during the year as a whole.[3,38-41]

Factors affecting the accuracy of estimation of exposures decades ago based on current measurements have been studied with data from Sweden.[42] The most important sources of uncertainty appear to be measurement errors and extrapolation from a rather short-term measurement to exposure over a long period. Measurements of Swedish residences today probably overestimate earlier levels of exposure.[43,44] Using this information and data from other studies,[45,46] we believe there has been an average increase of 10 to 20 percent in the radon concentration, weighted for changes in the housing stock, from the time the study subjects lived in the dwellings until the time the measurements were carried out.

As a rule, the radon concentration decreases when a window is kept open. A window ajar can provide an exchange of 10 to 30 cubic meters of air per hour at a wind velocity of 3 m per second.[47] This may be two to three times the normal rate of air exchange and thus may reduce the radon concentration by 50 to 70 percent.[3,41] No data on sleeping near an open window were obtained at the time of radon measurements, however. There may have been a degree of exposure misclassification due to this factor.

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COMMUNITY OUTBREAKS OF ASTHMA ASSOCIATED WITH INHALATION OF SOYBEAN DUST

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Abstract Since 1981, 26 outbreaks of asthma have been detected in the city of Barcelona. The geographic clustering of cases close to the harbor led us to consider the harbor as the probable source of the outbreaks. We therefore studied the association between the unloading of 26 products from ships in the harbor and outbreaks of asthma in 1985 and 1986.

All 13 asthma-epidemic days in these two years coincided with the unloading of soybeans (lower 95 percent confidence limit of the risk ratio, 7.2). Of the remaining 25 products, only the unloading of wheat was related to the epidemics of asthma, although when adjusted for the unloading of soybeans the relation was not statistically significant. High-pressure areas and mild southeasterly to southwesterly winds, which favored the movement of air from the harbor to the city, were registered on all epidemic days. Particles of starch and episperm cells that were recovered from air samplers placed in the city had morphologic characteristics identical to those of soybean particles. Furthermore, the lack of bag filters at the top of one of the harbor silos into which soybeans were unloaded allowed the release of soybean dust into the air.

We conclude that these outbreaks of asthma in Barcelona were caused by the inhalation of soybean dust released during the unloading of soybeans at the city harbor. (N Engl J Med 1989; 320:1097-102.)

OUTBREAKS of asthma characterized by short-term increases in emergency admissions for severe asthma have been reported in various parts of the world.[1-7] Although castor-bean dust has been reported to be a specific cause of asthma epidemics,[8-10] the causes of most other asthma epidemics remain controversial.[11]

Since 1981, 26 outbreaks of asthma have occurred in the city of Barcelona, affecting a total of 687 persons and causing 1155 emergency room admissions (mean number of admissions per outbreak, 44.4; range, 12 to 96). Between 1981 and 1984, outbreaks were identified by hospital-based clinicians who documented that on eight different days, sudden increases in emergency room admissions for acute severe asthma had overwhelmed the emergency services.[12,13] Informing public health officials of these episodes led to the development of the Asthma Collaborative Group of Barcelona, which designed a monitoring system to record all asthma emergencies on a daily basis, beginning in 1985.

A clustering of the asthma cases geographically, in time, and in both time and space simultaneously was noted during all the outbreaks. The observations strongly suggested that the outbreaks were caused by an agent released from a point source.[14,15] The geographic clustering of asthma cases next to the harbor and near an industrial area led us to consider these places as possible sources of the outbreaks.[14,15] The data did not support an association between the outbreaks of asthma and short-term increases in levels of air pollution.[14-16]

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During 1987 a coincidence between the unloading of soybeans in the harbor and outbreaks of asthma was observed. In this study we investigated the association between the unloading of products in the harbor, particularly soybeans, and the occurrence of asthma epidemics during the years 1985 and 1986.

METHODS

Identification of Asthma-Epidemic Days

All daily emergency room admissions of Barcelona residents with asthma were recorded during 1985 and 1986. Data were collected from the clinical records of the four largest urban hospitals, which account for approximately 90 percent of the emergencies in the city. An emergency room admission for asthma was defined as a visit during which any asthma-related diagnosis was recorded.[16] "Asthma" refers to a disease in which wide variations in resistance to flow in the airways of the lungs occur over short periods.[17]

The present study included only patients over 14 years of age, because no abnormal increases in the number of cases of acute severe asthma in childhood had ever been observed in the pediatric emergency services in Barcelona.[14,15]

An "unusual asthma day" was defined as a day on which the number of emergency room visits was so high that the probability that such a number or a higher one was the result of chance was 0.025 or less. This probability was calculated by assuming a Poisson distribution, with the 15-day moving average representing the number of cases expected.[18]

An "asthma-epidemic day" was defined as an unusual asthma day on which the cases were clustered on an hourly basis. An "hourly cluster" was defined as the occurrence in one four-hour period of so many emergency visits for asthma that the probability that such a high number of visits was the result of chance was 0.05 or less. The four-hour periods were selected on the basis of the distribution of cases during asthma outbreaks. This probability was calculated by the Knox and Lancashire approximation[19] to the scan method.[20]

Data on Products Unloaded at the Harbor

All products identified as having been loaded or unloaded during at least one asthma outbreak were studied. We recorded the days on which each product was loaded or unloaded during 1985 and 1986. In the case of soybeans, additional variables were examined, including the use of two harbor silos (A and B) for soybean storage, the form of the soybeans (in bulk, or as derivatives in the form of meal or pellets), and the country of the port of origin.

Table 1. Emergency Room Admissions during Outbreaks of Asthma in Barcelona, 1985–1986.

DATE	TOTAL DAILY ADMISSIONS			ADMISSIONS WITHIN A 4-HOUR PERIOD	
	ACTUAL	EXPECTED*	P VALUE	ACTUAL	P VALUE
1985					
7/10	17	5.6	<0.001	9	<0.001
8/21	12	3.9	<0.001	8	<0.01
9/10	14	5.3	<0.01	8	0.017
9/12	24	5.8	<0.001	13	<0.001
9/13	17	5.3	<0.001	7	0.016
9/23	17	4.8	<0.001	7	<0.01
1986					
1/21	96	11.8	<0.001	49	<0.001
5/6	34	6.9	<0.001	10	<0.01
5/7	15	6.3	<0.01	12	<0.001
9/17	33	6.8	<0.001	10	<0.001
11/11	54	10.5	<0.001	23	<0.001
11/24	32	7.7	<0.001	22	<0.001
11/25	18	6.9	<0.001	9	0.015

*Values are the number of admissions expected on the basis of a 15-day moving average.

Table 2. Association between Asthma Epidemic Days ("Asthma Days") and Various Products That Were Unloaded in the Harbor, over the 730-Day Period Studied.

PRODUCT	UNLOADING		NO UNLOADING		RISK RATIO	95 PERCENT CONFIDENCE INTERVAL
	TOTAL DAYS	ASTHMA DAYS	TOTAL DAYS	ASTHMA DAYS		
Soybeans	262	13	468	0	UH*	7.17–UH*
Wheat	30	3	700	10	7.0	2.33–20.99
Cement	503	12	227	1	5.42	0.89–32.00
Potassium chloride	511	11	219	2	2.36	0.55–10.04
Petroleum	56	2	674	11	2.19	0.51–9.39
Phosphates	217	6	513	7	2.03	0.70–5.84
Gas	229†	6	500†	7	1.87	0.65–5.42
Coal	200	4	530	9	1.18	0.37–3.78
Fuel oil	153	3	577	10	1.13	0.32–4.06
Cotton	406	7	324	6	0.93	0.32–2.74
Coffee	305	5	425	8	0.87	0.29–2.64
Minerals‡	276	4	454	9	0.73	0.23–2.34
Gasoline	182	2	548	11	0.55	0.13–2.39
Chemicals§	548	8	182	5	0.53	0.18–1.58
Corn	136	1	594	12	0.36	0.05–2.53
Butane	141	1	589	12	0.35	0.05–2.40

*UH denotes unquantifiably high.

†Value for one day is missing.

‡Including pyrite, perlite, bauxite, and granite.

§Including acetone, ethylene, kerosene, latex, perchloroethylene, sulfuric acid, styrene, and vegetable oils.

Aerobiologic and Meteorologic Data

During three nonconsecutive outbreaks — on November 11, 1986, February 8, 1987, and September 7, 1987 — particles were collected in small samplers with cellulose ester filters[21] placed in the district bordering the harbor, where most cases had occurred. Morphologic analysis was performed by optical microscopy on mineral oil–mounted slides. Lugol's solution was used for starch staining, and Coomassie blue solution for the detection of protein.[22,23] Soybean samples, collected from the hold of the ship that had unloaded soybeans during the two most recent documented outbreaks (September 4 and 7, 1987), were examined by optical microscopy and transmission and scanning electron microscopy.[22,23] Meteorologic information was collected on epidemic days from four stations in different parts of the city and a fifth at the airport, 5 miles to the southwest.

Statistical Analysis

For each product unloaded, a risk ratio was calculated between the probability of an asthma epidemic on the days when the product was being unloaded and the probability of an epidemic on the days when it was not being unloaded. The unit of observation and analysis was the 24-hour day.

Confidence intervals for the risk ratios were estimated by the Miettinen method.[24] When there was a zero in one cell of the two-by-two table, the lower limit of the confidence interval was calculated with use of the exact confidence-limit test[25]; in such a case, the null hypothesis was also tested with Fisher's exact test.[26] Evaluations of the independent effect of each product on the occurrence of asthma epidemics, with control for the other products, were carried out with use of the Mantel–Haenszel method.[27]

RESULTS

Thirteen of 23 "unusual asthma days" identified during the study period had hourly cluster patterns

Table 3. Association between Asthma Days and the Unloading of Soybeans, According to Unloading Site and Soybean Characteristics.

Variable	Asthma Days (N = 13)	Total Days (N = 730)	Lower Confidence Limit*	P Value
No unloading	0	468	—	—
Unloading				
Silo				
A	9	88	14.57	4×10^{-8}
B	1	132	0.16	0.22
Both	3	42	6.71	5×10^{-4}
Soybean type				
Bulk	13	237	7.96	5×10^{-7}
Derivatives	0	15	—	—
Both	0	10	—	—
Bulk soybeans in silo A	9	69	19.03	$<10^{-8}$
Country of origin				
United States	9	148	8.37	2×10^{-6}
Brazil	3	86	3.22	3×10^{-3}
Argentina	1	20	1.23	0.041
Brazil and Argentina	0	8	—	—

*Values are the lower limits of the 95 percent confidence intervals for the risk ratios.

and were classified as asthma-epidemic days (Table 1). All 13 asthma-epidemic days coincided with the unloading of soybeans, whereas no epidemic days occurred when soybean unloading did not take place. A risk ratio significantly higher than 1 was obtained only for soybeans and wheat (Table 2). The risk ratio for soybeans was too high to be quantifiable (lower limit of the confidence interval, 7.17). Only 3 of 13 asthma-epidemic days coincided with the unloading of wheat (risk ratio, 7.0; 95 percent confidence interval, 2.33 to 20.99). After adjustment for the unloading of soybeans, the risk ratio for wheat was lower (risk ratio, 5.03; 95 percent confidence interval, 0.95 to 26.46).

When the site of soybean unloading (silo A or B) was taken into account, the association was statistically significant for silo A ($P<0.001$), but not for silo B ($P = 0.22$). All the outbreaks occurred when soybeans were unloaded in bulk form, not as meal or pellets. Furthermore, there was a statistically significant relation between the unloading of soybeans and the asthma epidemics, regardless of the country of the port of origin of the soybeans (Table 3).

The daytime wind patterns remained constant throughout the epidemics, characterized by mild southeasterly to southwesterly winds (less than 5 m per second on all epidemic days except for one day on which the maximal speed was 6.1 m per second). There were periods of no wind at all. The epidemics occurred on days of high barometric pressure. The temperature (range of low temperatures, 8 to 21°C) and relative humidity (range, 46 to 70 percent) varied widely among the epidemic days.

In the air filters collected on the epidemic days, spheroidal particles that were positive for Lugol's solution and Coomassie blue solution were found (about 380 particles per cubic meter). They were identified as starch. Large, trumpet-shaped cells (soybean-wall cells) were also recovered (Fig. 1). On analysis, the bulk soybeans collected directly from the hold of the ship that had unloaded soybeans had surface aggregates of starch particles. Large, trumpet-shaped cells, morphologically identical to those in the filters, were also found in the episperm of cross-sectioned soybeans (Fig. 2).

Discussion

There was a strong association between the asthma-epidemic days and the unloading of soybeans in bulk form. No epidemics occurred when soybeans were not being unloaded. Of the remaining 25 products investigated, only the unloading of wheat was related to asthma epidemics, but less strongly so than the unloading of soybeans.

The finding of this association could have been biased by a misclassification in the determination of epidemic and nonepidemic days. Asthma-epidemic days were determined on the basis of two objective criteria — an unusually large number of emergency cases of acute severe asthma, and an hourly cluster of cases. The method of recording "unusual asthma days" was developed by Goldstein and Rausch and was used to detect asthma epidemics in New York[18] and New Orleans,[28] having been recommended as a method of epidemiologic surveillance.[29] The criterion

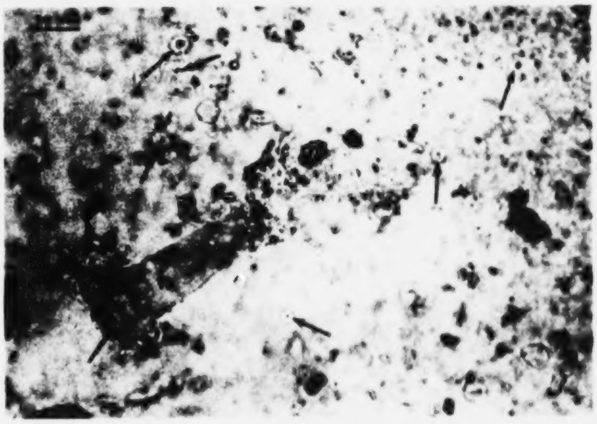

Figure 1. Optical-Microscope Image of the Filter of an Air Sampler Placed in the City during an Epidemic Day.

Starch particles (arrows) and soybean-wall cells (trumpet-shaped cells [TS]) are visible.

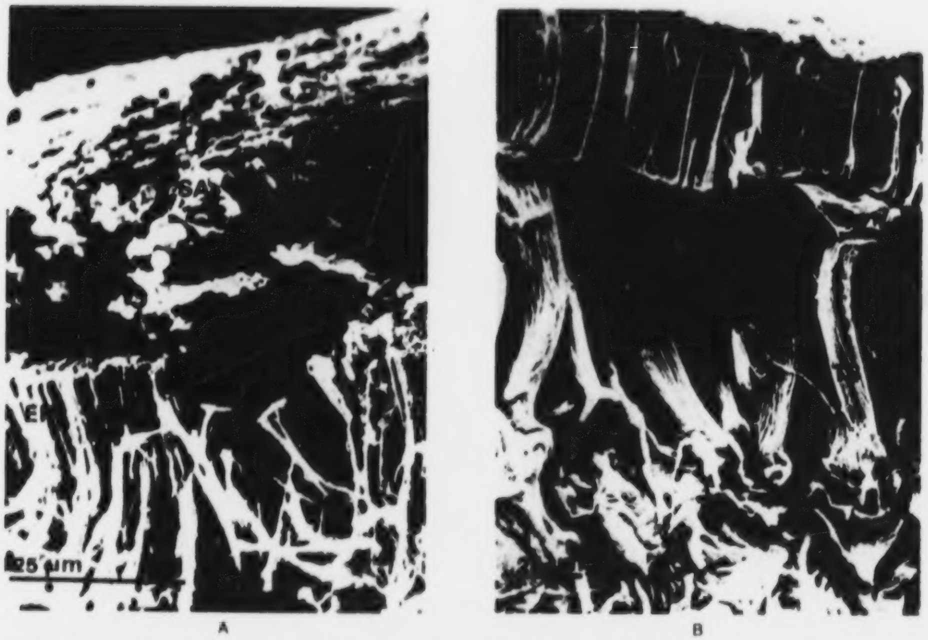

Figure 2. Scanning-Electron-Microscope Images of the Cross Section of a Soybean from the Hold of a Ship from Which Soybeans Were Unloaded on an Epidemic Day.

Starch aggregates (SA) and soybean-wall cells (episperm cells [EP]) appear in Panel A, and episperm cells and trumpet-shaped cells (TS) appear in Panel B.

of hourly clusters was used to discriminate asthma-epidemic days from the unusual asthma days that would be expected to occur normally by chance. Since the asthma-epidemic days were identified before we developed our hypothesis about soybean dust[10] and also before the data on soybean unloading were collected, a bias in the direction of a strong effect of soybean dust seems unlikely.

Although outbreaks of asthma were noted in Barcelona from 1981 to 1987, the present study covered only the 1985–1986 period, for which complete monitoring data were available. The fact that all known outbreaks of asthma since 1981 occurred on days when soybeans were unloaded strongly suggests that the analysis of a more extended period than 1985–1986 might yield similar results.

The lack of temporal independence in both variables — unloading of soybeans and outbreaks of asthma — may have biased the estimated significance of the risk ratio. However, the strong association between the variables makes it unlikely that this problem would explain the high degree of association found. In addition, the association between the unloading of soybeans and the outbreaks of asthma remained statistically significant when we adjusted for autocorrelation[11,12] (and unpublished data).

We observed a significant difference between the risk ratios associated with the unloading of soybeans into the two silos, A and B. Silo A was closer than silo B to the urban area in which the asthma outbreaks most frequently occurred. Although both silos used the same unloading procedure (soybeans were unloaded by a vacuum system, raised to the top of the silo, and thrown down into it), silo A was higher than silo B (70 as compared with 20 m), and unlike silo B, it did not have bag filters installed in the cyclone dust-collection system, thereby allowing the release of large amounts of soybean dust into the air.

High barometric pressure and low southeasterly to southwesterly wind speeds were registered on epidemic days — appropriate weather conditions for moving air from the harbor to the city. High-pressure areas with still air have been identified in other asthma outbreaks, such as those in New Orleans[13] and New York City.[14]

Likewise, the conclusion that soybean dust reached the city is supported by the morphologic similarity between the starch particles and trumpet-shaped cells recovered from the air samplers and those recovered from the cargo hold, together with the placement of the samplers close to the harbor and inside the urban district in which most cases of asthma were registered. Spheroidal particles identified as starch have already been described as a component of soybean dust.[22]

All the above findings led us to conclude that the unloading of soybeans gave rise to a sudden, massive release of soybean dust that reached the urban area under appropriate meteorologic conditions and caused the outbreaks. In addition, a preliminary analysis of the data on asthma emergencies in Barcelona each day during the 16-month period after the installation of appropriate bag filters at silo A (September 1987) indicates that outbreaks of asthma have disappeared completely.

These results are consistent with those obtained in a serologic case–control study that we carried out recently.[35] In 64 of 86 cases occurring during asthma epidemics (74.4 percent), a reaction with commercial soybean-antigen extracts was shown, as compared with only 4 of the 86 matched controls (odds ratio, 61; lower limit of the 95 percent confidence interval, 8.07). No other serologic covariates (total serum IgE levels or specific IgE levels against the most common airborne allergens or legumes) confounded the association between serum antisoybean IgE antibodies and epidemics of asthma. In addition, preliminary characterization of the antigens involved in the outbreaks of asthma in Barcelona has shown that the patients with asthma reacted specifically to an acidic and low-molecular-weight protein band of the dust and hull of the soybean (Morell F, Rodrigo MJ: personal communication).

Asthma epidemics have been described in other cities, including New Orleans,[2] New York,[1] and Birmingham, England,[5] but their specific causes have been controversial. Only castor-bean dust has been reported to be specifically causative of asthma epidemics.[8-10] In New Orleans, the marked decline in asthma outbreaks has recently been attributed both to better socioeconomic conditions and the availability of better medical care for indigent patients with asthma, rather than to the disappearance of specific allergens or industrial chemical pollutants.[11] In New York City, asthma-epidemic days were more likely to occur when susceptible persons spent more time indoors, suggesting an exposure to agents in the home.[28] No relation was found, however, between outdoor air pollution and outbreaks of asthma,[36] as in Barcelona.[16] In Birmingham, a large asthma outbreak appeared to be caused by *Didimella exitialis*,[5] but a more recent study could not confirm this hypothesis,[37] and the question of the origin of the epidemic remains open.[38]

Soybeans have been identified as causing bronchial asthma, although infrequently so. Most of the cases reported were among mill workers,[39-44] and soybean dust is included among the occupational causes of asthma.[45-47] Both the frequency of the Barcelona epidemics and the large number of persons affected contrast sharply with the relatively few cases reported hitherto. This unusual epidemiologic presentation may be explained, at least in part, by several local factors: the harbor borders the most densely populated district of the city, soybean dust was released during unloading because of the lack of bag filters in a silo, and outbreaks occurred on days when weather conditions favored the transportation of dust to the city. These conditions may not be unique to Barcelona, and we recommend that whenever outbreaks of asthma occur, the release of soybean dust be considered as a possible cause.

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ATSDR June1990
Case Studies in Environmental Medicine

9

Tetrachloroethylene Toxicity

Environmental ALERT . . .

☑ *Tetrachloroethylene is used mainly as a solvent for dry cleaning and metal degreasing.*

☑ *Like most chlorinated solvents, tetrachloroethylene can cause CNS depression.*

☑ *Chronic exposure to tetrachloroethylene may adversely affect the neurologic system and liver.*

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. The Agency for Toxic Substances and Disease Registry (ATSDR) and the Centers for Disease Control (CDC) designate this continuing medical education activity for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association and 0.1 continuing education units for other health professionals. See pages 21 to 23 for further information.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

Headache, decreased concentration, and irritability in a 37-year-old silk screener

A 37-year-old woman who is 4 months postpartum is seen at your office with complaints of headache, increasing irritability, and difficulty concentrating. She states that she has become impatient and short-tempered with her husband and new child; minor things make her angry. These feelings began about 1 month ago. She is most aware of them in the evenings, when they are sometimes accompanied by a throbbing frontal headache. She has no psychiatric history but admits to drinking 3 ounces of alcohol a day since being married, 4 years ago. She did not drink during the pregnancy and denies using other drugs or medications. She has had no trouble sleeping.

Two weeks ago the patient and her family visited her parents for a week. During that time she felt well; the irritability and headaches subsided. Since coming home last week, however, the symptoms have returned.

The patient is worried that something in the home is causing her symptoms. She reports that the house was sprayed for termites 2 years ago, but she does not remember the name of the fumigant used. Her husband feels fine and has not been ill. Her infant daughter's delivery was uneventful and the baby appears to be developing normally but has been "very fussy" lately. The infant, whom you saw 5 weeks ago for otitis media, is still breastfeeding.

A month ago the patient returned to her job as a word processor, working mornings and relaxing with her hobby, silk screening, in the afternoon. She gets along well with her employer and fellow employees, and the job is not generally stressful. However, she is concerned that a loss in typing accuracy and a decreased ability to concentrate may lead to conflict with her supervisor. The patient has no symptoms of postpartum depression and had no history of headaches before she resumed these activities.

On physical examination you find a slightly overweight woman with blood pressure of 125/85. Pulse is 68 and regular. She is afebrile. Her nail beds are pale. There are no skin rashes, lesions, or stigmata of liver disease. The conjunctiva are mildly injected, but the nares and oral mucosa are not swollen or injected. The thyroid is not enlarged, and no lymphadenopathy is present. There is no focal muscle tension or tenderness. There is no hepatomegaly; examination of the abdomen is unremarkable. Neurologic examination is within normal limits. Recent and distant memory are intact, proverb interpretation is normal, and she is able to do serial 7s. Sensory and motor examination are normal, as are Romberg test and gait. Deep tendon reflexes are normal and symmetrical.

Pretest

(a) *What should be included in this patient's problem list?*

(b) *What further information would assist in establishing a diagnosis?*

(c) *What laboratory tests would you order for this patient?*

Answers to the Pretest can be found on page 18.

Exposure Pathways

- **Tetrachloroethylene is used mainly as a solvent for dry-cleaning textiles and for cleaning metal parts.**
- **It is also found as an ingredient in a number of consumer products such as fabric cleaners and spot removers.**

Tetrachloroethylene is a clear, colorless, nonflammable liquid having a sweet, fruity odor like chloroform. It is volatile and readily evaporates at room temperature. Tetrachloroethylene is used mainly for textile processing and dry-cleaning fabric (about 53% of total U.S. usage), for degreasing and drying metal parts (10%), and for manufacturing other solvents such as freons (28%). It is used as a solvent and cleaner in consumer formulations including auto brake cleaners, suede protectors, paint removers, water repellents, silicone lubricants, belt lubricants, adhesives, spot removers, wood cleaners, and many products used by hobbyists. Chemical synonyms for tetrachloroethylene include tetrachloroethene, perchloroethylene, 1,1,2,2-tetrachloroethylene, and ethylene tetrachloride. Other commonly used names are perchlor, perc, PCE, tetra, and perclene.

Tetrachloroethylene exposure can result from environmental as well as occupational sources. It is released to air and water by evaporation or fugitive emissions from industrial and dry-cleaning plants, and from landfills where it may be stored. An estimated 80% to 85% of the tetrachloroethylene produced in the United States is eventually released to the environment.

Evaporated tetrachloroethylene collects in the atmosphere and degrades only slowly. Average air levels in the United States range from 0.16 parts per billion (ppb) in rural areas to 1.3 ppb in areas near storage or utilization sites. Some of the tetrachloroethylene in air is carried to the ground through rainwater.

Up to 25% of the water supplies in the United States have detectable levels of tetrachloroethylene, ranging from 0.01 to 1500 ppb, with the highest levels found in aquifers fed by significantly contaminated groundwater. Industrial operations, such as auto engine cleaning, dry cleaning/laundering, aluminum forming, metal finishing, and chemical/plastic manufacturing, may discharge tetrachloroethylene in wastewater at levels exceeding 1 part per million (ppm).

Tetrachloroethylene has been used as an anthelmintic in humans and animals. In soft gelatin capsules, it is effective as an ascaricide for swine, as treatment for stomach worms in sheep, and for the elimination of nematodes (hookworm) in all species including humans. Since more effective and less toxic agents are currently available for these indications, tetrachloroethylene is now seldom used in the United States as a therapeutic agent, and then only for veterinary applications.

Challenge

(1) Additional information for the case study: On questioning, your patient explains that silk screening involves stretching a large piece of cloth across a form, like a picture frame, masking it to create a pattern, then dying the unmasked areas. Before masking the cloth, it must be cleaned. The patient mentions that she just started using a new fabric cleaner about 5 weeks ago. Her cousin, who also enjoys silk screening, assured her it was harmless and the best available. The product is called "Clean Cloth," but the patient can remember little else about it.

Assuming the label on the "Clean Cloth" container does not list the contents, how will you determine the ingredients of this consumer product?

Who's at Risk

An estimated 500,000 workers in the United States may be at risk of exposure to tetrachloroethylene; many of these workers are employed in the 20,000 dry-cleaning establishments in this country. A NIOSH survey of 44 dry-cleaning facilities found air levels of tetrachloroethylene ranging from 4 to 149 ppm in the shop areas and from 0.5 to 3.1 ppm at the front counter. Much higher tetrachloroethylene levels are associated with cleaning spills or replacing dry-cleaning filters. (The current permissible workplace exposure level as promulgated by the Occupational Safety and Health Administration [OSHA] is 25 ppm averaged over an 8-hour workshift.) Increased opportunity for exposure may also be encountered by machinists, plastic extruders, and electronic assemblers, and by workers manufacturing consumer products containing tetrachloroethylene.

Exposures to consumer products containing tetrachloroethylene have led to acute toxicity. Accidental ingestions or spills, and use of products in small, enclosed spaces may place unsuspecting persons at risk. For example, a spot remover containing tetrachloroethylene used to clean a carpet in a poorly ventilated area can produce dangerously high air levels. Clothes, drapes, or other re-

- ☐ **Workers in industries such as dry cleaning, machining, and electronics, as well as consumers who use tetrachloroethylene-containing products have an increased likelihood of exposure.**
- ☐ **Persons using well water contaminated with tetrachloroethylene can be exposed by inhalation as well as ingestion.**
- ☐ **Tetrachloroethylene crosses the placenta and can be found in breast milk; therefore, the fetus and nursing newborn may be at increased risk of adverse effects from maternal exposure.**

cently dry-cleaned fabrics may release tetrachloroethylene for several hours. The death of a teenaged boy has been attributed to tetrachloroethylene intoxication from an inadequately aired sleeping bag dry-cleaned a short time before use, and a patient was reported to develop stupor and coma after inhaling tetrachloroethylene vapors from clothes cleaned in a self-service dry-cleaning machine.

Generally, environmental background levels of tetrachloroethylene in urban air and water are low and have not been known to cause adverse effects. Low levels of tetrachloroethylene were found in the exhaled breath of teachers and children at a kindergarten located near a factory using the chemical, and in the residents of a retirement home located near a former chemical waste dump. Occasionally, well water is contaminated with tetrachloroethylene at significant levels; exposures in these cases can occur by inhaling vapors during bathing or laundering, and by drinking the water.

Data from animal and human studies indicate that tetrachloroethylene crosses the placenta. Although effects are uncertain, this ease of distribution may place the fetus at increased risk. In addition, tetrachloroethylene, like most other chlorinated chemicals, can be transmitted in breast milk, thus subjecting the nursing newborn to continued exposure. In one case report, a nursing mother, who had been repeatedly exposed to tetrachloroethylene fumes during lunch-hour visits with her husband at a dry-cleaning plant, had tetrachloroethylene levels of 300 µg/dL in blood and 1000 µg/dL in breast milk. The nursing infant developed obstructive jaundice, possibly as a result of tetrachloroethylene exposure.

Challenge

(2) The certified poison control center in your region informs you that "Clean Cloth" is 90% tetrachloroethylene and 10% Freon-22 (dichlorodifluoromethane). Might the infant described in the case study be at increased risk? Explain.

Biologic Fate

In humans, about 70% of an inhaled tetrachloroethylene dose is absorbed by the lungs, and about 80% of an oral dose is absorbed by the gut. Tetrachloroethylene penetrates human skin slowly. Once tetrachloroethylene is absorbed, it is readily distributed to all body tissues. Because it is highly lipid-soluble, it tends to concentrate primarily in adipose tissue.

More than 80% of inhaled tetrachloroethylene is eliminated unchanged by the lungs. With minimal physical activity, elimination of tetrachloroethylene from blood occurs in a biphasic pattern. In one study, the average half-life of each phase was 2.6 hours and 33 hours, respectively. The average half-life of tetrachloroethylene in adipose tissue is about 72 hours.

Less than 2% of absorbed tetrachloroethylene is metabolized in the liver to trichloroacetic acid and trichloroethanol, which are then excreted in the urine. The rate of urinary elimination is slower than the exhalation rate, with urinary biologic half-lives ranging from 12 to 55 hours for the first phase, and 100 to 200 hours for the second phase. Studies of dry-cleaning shop workers have shown that urinary metabolite levels increase linearly with air concentrations up to 100 ppm tetrachloroethylene, then level off at higher concentrations. This indicates the saturability of the tetrachloroethylene metabolic pathways.

- ☐ **Tetrachloroethylene does not bioaccumulate in the food chain.**
- ☐ **Most absorbed tetrachloroethylene is excreted unchanged in the breath; a small amount is metabolized in the liver and excreted in urine as trichloroacetic acid and trichloroethanol.**
- ☐ **The elimination of tetrachloroethylene and its metabolites appears to be biphasic, with a rapid first phase (hours), and a second slow phase (days).**

Challenge

(3) How could you determine if a patient has been exposed to tetrachloroethylene?

Physiologic Effects

Exposure to tetrachloroethylene has resulted in effects on the central nervous system (CNS), skin, mucous membranes, eyes, lungs, liver, and kidney. CNS effects have been noted most frequently.

Acute Exposure

☐ **As with most chlorinated solvents, acute exposure to tetrachloroethylene primarily affects the CNS and causes skin, throat, and eye irritation.**

Acute exposure to tetrachloroethylene at air levels of 75 to100 ppm causes irritation of the eyes and upper respiratory tract. Minor CNS effects have also been observed with acute inhalation exposures from 100 to 300 ppm. At the latter levels, the Romberg test may be positive and results of certain coordination and behavioral tests may be abnormal. At higher air levels, unconsciousness can occur.

Acute tetrachloroethylene ingestion rarely occurs, but as much as 500 mg/kg did not cause death in one case, and, in another case, CNS depression was noted with ingestion of 4.2 to 16 g. Up to 16 g has been ingested without causing liver or renal injury.

Chronic Exposure

☐ **Besides affecting the CNS and skin, tetrachloroethylene may adversely affect the liver, kidneys, and possibly the heart.**

Chronic exposure to tetrachloroethylene may have adverse effects on the skin and hepatic, renal, and nervous systems. Although tetrachloroethylene causes cancer in animals, it has not been established as a human carcinogen. Nevertheless, based on the weight of evidence in animals, the U.S. Environmental Protection Agency (EPA) classifies tetrachloroethylene as a probable human carcinogen. Insufficient data are available to judge whether tetrachloroethylene adversely affects reproductive and developmental outcomes in humans.

Nervous System Effects

☐ **CNS effects are generally reversible on cessation of exposure.**

Persons chronically exposed to tetrachloroethylene may experience short-term memory deficits, ataxia, irritability, disorientation, and sleep disturbances. In one case, the owner of a dry-cleaning shop in business for 30 years was diagnosed with progressive dementia. His serum tetrachloroethylene level was 75 µg/dL, whereas serum levels rarely exceed 5 µg/dL in the general population.The patient's short-term memory impairments gradually cleared over several months after exposure to tetrachloroethylene ceased. Some patients may be mistakenly diagnosed with Alzheimer's disease or other CNS disorders when, in fact, they have a preventable and possibly reversible condition.

Hepatic and Renal Effects

Tetrachloroethylene is considered a weak hepatotoxin based on case reports of human exposure. Hepatitis, cirrhosis, liver cell necrosis, hepatomegaly, and elevated liver function indices have been noted. Most reported cases are due to accidental exposures or deliberate abuse of unknown dose and duration. Mild transient increases in serum transaminase values have occurred as a result of a severe, brief exposure in adults; organ dysfunction has been noted only after months of exposure at levels in excess of 100 ppm. In animal studies, intermittent exposures to air levels as low as 9 ppm tetrachloroethylene have produced irreversible hepatic injury.

Nonproliferative kidney lesions are characteristic of other chlorinated compounds with similar chemical structure; thus, tetrachloroethylene should be regarded as a possible nephrotoxic agent in humans. Nephrotoxicity or hepatotoxicity would not be expected, however, from exposure at environmental levels or at the current permissible workplace level.

☐ **Hepatic and renal toxicity may occur in humans exposed to tetrachloroethylene.**

Cardiac Effects

The cardiac effects of tetrachloroethylene in animals have been studied extensively. In some anesthetized species, high levels of tetrachloroethylene increased the vulnerability of the ventricles to epinephrine-induced extra-systoles, bigeminal rhythms, and tachycardia. In one study, ventricular dysrhythmias occurred in approximately 30% of the anesthetized animals after injection of tetrachloroethylene alone. The effects of agents with anesthetic properties, however, may be indistinguishable from the effects of anesthesia-related hypoxia and acidosis.

Tetrachloroethylene may be associated with cardiotoxicity in some persons. One case has been noted of a dry cleaner who had symptomatic ventricular ectopy that temporally correlated with elevated plasma tetrachloroethylene levels during work. He may have been particularly sensitive to tetrachloroethylene, however, since no similar cases have been reported.

☐ **Tetrachloroethylene may affect the heart; however, no deaths due to cardiotoxicity have been reported in workers.**

Reproductive and Developmental Effects

Tetrachloroethylene did not cause birth defects in exposed rats and mice. It was associated with lower fetal weights, but only at exposure levels that were also toxic to the dams. The few studies of tetrachloroethylene's effects on human reproductive outcomes are inconclusive, although they suggest that adverse reproductive or developmental effects might occur.

☐ **No teratogenic effects of tetrachloroethylene have been found in experimental animals.**

Male workers exposed to tetrachloroethylene have not displayed reproductive effects. Maternally absorbed tetrachloroethylene is known to cross the placenta and can also be transmitted to the nursing newborn in milk. Women who regularly work with the chemical should avoid excessive exposures and should not breast-feed. The 6-week-old infant described on page 4, who developed obstructive jaundice and hepatomegaly, improved clinically after breast-feeding was discontinued; liver function was normal during 2 years of follow-up.

Carcinogenic Effects

☐ **Conclusive proof of the carcinogenic potential of tetrachloroethylene in humans is lacking.**

Some epidemiologic studies of dry-cleaning workers have suggested a possible association between chronic tetrachloroethylene exposure and increased cancer risk. Studies have reported lymphoma and various cancers of the lung, larynx, skin, cervix, uterus, liver, kidney, and bladder. The results have been judged inconclusive because these studies were based on inadequate information of the degree of exposure and investigators were unable to control for smoking, socioeconomic status, and exposure to other solvents.

In studies using mice or rats, high-dose oral administration of tetrachloroethylene was associated with an increased incidence of hepatocellular carcinoma, and inhalation exposure was associated with leukemia, renal tubular cell adenomas, and adenocarcinomas. Data from animal studies, together with supporting data on tetrachloroethylene mutagenicity, constituted a sufficient level of evidence for EPA to classify tetrachloroethylene as an animal carcinogen and a probable human carcinogen.

Challenge

(4) What will you tell your patient regarding the hazards of tetrachloroethylene?

Clinical Evaluation

History and Physical Examination

The physician should ask about previous occurrences of similar symptoms. If a temporal association between symptoms and exposure to certain products is suspected, an attempt should be made to identify the specific chemical ingredients involved. If the product label does not list the chemical ingredients, the regional poison control center may maintain a list of ingredients in consumer and proprietary products. In occupational exposures, the employer or manufacturer is required by law to provide a material safety data sheet (MSDS), which lists the chemical ingredients and describes their potential toxicity.

It will be helpful to know if other family members or coworkers have similar symptoms. It is also important to note the time of last exposure to a suspected chemical since a temporal relationship between onset of symptoms and work or other activity may provide important clues. One should also evaluate general health and question the patient regarding alcohol and drug use.

Eyes, nose, throat, and skin should be examined carefully for inflammation or irritation. The conjunctiva may be injected, and nasal mucosa, may be injected and swollen. Repeated inhalation exposures to tetrachloroethylene can cause defatting of nasal mucosa, leading to a friable condition with drying, cracking, or bleeding. Skin contact may cause dermatitis by irritation and defatting.

A complete neurologic evaluation should be performed with special attention to memory, gait, and balance. Short-term memory loss, if associated with tetrachloroethylene exposure, is generally transient. In patients with acute exposures, the Romberg balance test has been positive. The patient should be examined for hepatomegaly. Vital signs should be recorded, especially abnormalities of heart rate or rhythm. Patients should be assessed for costovertebral angle tenderness, and the history should include any urinary abnormalities such as hematuria.

- ☐ **The physician should attempt to establish a temporal relationship between symptoms and exposure to tetrachloroethylene.**
- ☐ **Physical examination should include skin, ENT, liver, kidneys, and CNS.**

Signs and Symptoms

Acute Exposure

Background levels of tetrachloroethylene in air, water, and food have not been associated with symptoms. The odor threshold of tetrachloroethylene is reported to be from 5 to 50 ppm; symptoms

- ☐ **Odor may not provide adequate warning of toxic tetrachloroethylene levels.**

☐ **Effects of acute inhalation exposure include mucous membrane irritation and CNS depression.**

typically do not occur until approximately 75 ppm. Odor warning is not always reliable, however, because some people have a higher threshold of detection, and acclimatization to tetrachloroethylene can occur.

The principal symptoms of acute inhalation exposure are eye and upper airway irritation (at 75 to 100 ppm) and CNS depression (at 100 to 300 ppm). Eye instillation can lead to corneal burns and conjunctivitis; skin contact may result in inflammation or chemical burns. If tetrachloroethylene contacts fire or a hot metal surface, it can produce irritating or poisonous gases such as chlorine and phosgene.

The onset, intensity, and duration of symptoms can vary among identically exposed persons. The variability of toxicity is influenced by many factors such as respiratory rate, target organ sensitivity, body fat content, and general health. CNS symptoms can be similar to those of ethanol inebriation. Pulmonary edema has occurred in one laundry worker found unconscious after exposure to tetrachloroethylene vapor.

Symptoms associated with acute high-level tetrachloroethylene exposure may include the following:

Nervous system

Euphoria
Headache
Dizziness
Light-headedness
Sleepiness
Forgetfulness
Irritability
Slurred speech
Confusion
Loss of coordination
Loss of consciousness

Gastrointestinal

Nausea

ENT

Eye and nose irritation
Upper airway irritation and cough

Chronic Exposure

☐ **Chronic exposure may affect the skin, and neurologic and hepatic systems.**

Mild CNS symptoms are often reported in conjunction with exposure to tetrachloroethylene-containing household products in confined spaces, and with exposure in industrial settings. Workers' symptoms have included persistent headache, short-term memory deficits, ataxia, irritability, disorientation, and sleep disturbances. Evidence in volunteers and exposed workers indicates that levels of 25 ppm or less do not produce neurologic deficits or behavioral performance impairment.

The liver is the primary target organ in animals exposed chronically to tetrachloroethylene. In humans, chronic exposure has led to hepatitis and elevated transaminase levels (SGOT or AST and SGPT or ALT). Death due to hepatorenal failure has been reported only as a result of tetrachloroethylene abuse.

Dysrhythmia was noted in one worker exposed occupationally to tetrachloroethylene; no sudden deaths have been reported. Tetrachloroethylene's defatting action on skin may cause dermatitis, thereby predisposing the skin to infection.

Laboratory Tests

Direct Biologic Indicators

- **Tetrachloroethylene itself may be measured in breath and blood; its metabolites can be measured in blood and urine.**

In exposed persons, tetrachloroethylene may be measured in expired air and blood; its metabolite, trichloroacetic acid, may be measured in blood and urine. If the cause of symptoms is questionable, direct biologic testing may be warranted. However, other chemical exposures, such as to 1,1,1-trichloroethane and trichloroethylene, can also result in the presence of trichloroacetic acid in blood and urine. Trichloroethanol, another metabolite of tetrachloroethylene and trichloroethylene, has been reported, but not consistently, in urine of tetrachloroethylene-exposed workers. Trichloroethanol and trichloroacetic acid can also be found in patients taking chloral hydrate.

To measure tetrachloroethylene in blood or expired air, samples should be collected within 16 hours after exposure; urine tests will remain positive up to 5 days after exposure, depending on the dose. Few laboratories perform these specialized tests; regional poison control centers may be able to identify such facilities. The method of sampling and sample storage must be coordinated with the laboratory to ensure proper specimen collection and processing. The laboratory should provide reference values appropriate for the analytical method used, if they exist. Recording the time of sample collection relative to the last exposure is critical to interpretation of results.

Expired air and blood tetrachloroethylene levels and urine trichloroacetic acid levels have been linearly correlated with ambient air concentrations up to 100 ppm. In workers, a trichloroacetic acid level of 7 mg/L in urine obtained at the end of the workweek was found to correlate with exposure to an average of 50 ppm tetrachloroethylene for 1 week. The same exposure level will result in approximately 100 µg/dL tetrachloroethylene in blood drawn 16 hours after the last work shift of the week. Increased physical activity during exposure can result in higher levels.

Indirect Biologic Indicators

☐ **Significant exposure to tetrachloroethylene may result in elevated values of renal and liver function tests.**

Although tetrachloroethylene may cause upper airway irritation and coughing, the chest X ray or pulmonary function test will probably be normal. In general, results of routine laboratory tests, including renal and liver function tests, will also be normal unless the patient has had a significant exposure and has concurrent neurologic symptoms.

Transient elevation of transaminase levels has been reported in tetrachloroethylene exposures, but frank hepatic necrosis has not been documented. If a known acute exposure to tetrachloroethylene results in CNS symptoms such as syncope, then liver function tests, BUN, serum creatinine, and urinalysis should be obtained immediately to establish baseline. Testing should be repeated after several days to monitor for possible effects. Liver function tests should include SGOT (AST), SGPT (ALT), lactic dehydrogenase (LDH), bilirubin, and alkaline phosphatase. If levels are mildly elevated, tests should be repeated in several weeks to document return to baseline. If levels remain elevated, other causes of hepatic dysfunction should be investigated.

The value of a neuropsychologic evaluation for differentiating between organic and functional impairment is controversial, especially when no baseline evaluation is available. The tests, however, may be useful when comparing an exposed occupational population to a control group. Although neurologic tests provide "soft" data, they may be used to raise suspicion of cognitive impairments that are not evident on mental status testing, or as a baseline for follow-up.

Challenge

(5) What other history will help in determining if the neurologic symptoms of the patient described in the case study are due to "Clean Cloth"?

(6) The patient asks why her cousin, who uses "Clean Cloth" for the same purpose, has not been ill. What can you tell her?

(7) The patient's laboratory tests show urinary trichloroacetic acid of 4.2 mg/L immediately after a 1-week exposure and a slightly elevated SGOT and SGPT. How do you interpret these results?

Treatment and Management

Acute Exposure

No specific treatments are available for acute tetrachloroethylene exposures. Data from humans are insufficient to determine an ingestion level at which emesis should be induced. If a gag reflex is not apparent, emetics should not be administered because aspiration of gastric contents could result. Gastric lavage may be useful in recent, large ingestions. Although charcoal and cathartics may be given, their efficacy is not proven.

Contaminated clothing should be removed without endangering health care personnel. Supportive care directed to adequate ventilation and circulation should be provided. Moderately to severely exposed patients should have cardiac monitoring for potential dysrhythmias, and oxygen should be administered if respiratory depression has occurred.

- ☐ **There is no antidote for tetrachloroethylene toxicity; supportive measures should be administered.**
- ☐ **In a patient who ingested tetrachloroethylene, controlled hyperventilation therapy was apparently successful.**

Because more than 80% of tetrachloroethylene is eliminated in the breath, a proposed method of clearing it from the body in an acute exposure is through controlled hyperventilation. Hyperventilation therapy (volume 10 L/min) was used on a comatose 6-year-old, 2 hours after the child ingested 8 to 10 mL of pure tetrachloroethylene. The initial tetrachloroethylene blood level was 2150 µg/dL. On the fifth day, when hyperventilation was terminated, the blood level was less than 100 µg/dL. The child completely recovered. The effectiveness of hyperventilation in tetrachloroethylene overdose, however, has not been validated. Without experimental controls, the extent to which hyperventilation contributed to the boy's recovery remains uncertain.

CNS symptoms due to acute tetrachloroethylene inhalation exposure are transient but may linger for hours after exposure ceases. Patients usually recover rapidly without permanent neurologic sequelae if hypoxia and shock have been prevented.

Chronic Exposure

☐ **Long-term management requires reduction or elimination of exposure.**

Symptoms related to chronic exposure tend to worsen during exposure and improve over a weekend, on vacation, or with a job transfer. If there is no clear association between symptoms and exposure, other etiologies should be considered.

For persons with tetrachloroethylene toxicity, the level of exposure either must be reduced or the source eliminated. Substitution of an agent less hazardous than tetrachloroethylene may be feasible. It is important that substances containing tetrachloroethylene be handled in well-ventilated areas. High levels of exposure can occur during clean-up of contaminated equipment and spills, and may require use of an approved full facepiece self-contained breathing apparatus (SCBA) or similar device. Procedures for cleaning up spills should be established in advance. All containers of liquid tetrachloroethylene should be capped; rags soaked with tetrachloroethylene should be stored in sealed containers.

Challenge

(8) What recommendations can you make if the patient wishes to continue using "Clean Cloth"?

Standards and Regulations

Workplace

Air

OSHA has a maximum permissible exposure limit (PEL) in workplace air of 25 ppm measured as an 8-hour time-weighted average (TWA). This regulatory level was reduced from 100 ppm in 1989 (Table 1).

☐ **The current OSHA 8-hour TWA for tetrachloroethylene is 25 ppm.**

Table 1. Standards and regulations for tetrachloroethylene

Agency*	Focus	Level	Comments
ACGIH	Air -Workplace	50 ppm	Advisory; TLV-TWA†; STEL§ of 200 ppm
NIOSH	Air -Workplace	N/A	Advisory; lowest feasible level
OSHA	Air -Workplace	25 ppm	Regulation; PEL¶ over 8-hour workday
EPA	Air-Environment	None	Regulation under development; due early 1991
	Water-Environment	None	Regulation; proposed 5 ppb to take effect winter 1990

* ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration

† TLV-TWA (Threshold Limit Value–Time-Weighted Average) = time-weighted average concentration for a normal 8-hour workday and 40-hour workweek to which nearly all workers may be repeatedly exposed.

§ STEL (Short-Term Exposure Limit) = usually a 15-minute sampling period.

¶ PEL (Permissible Exposure Limit) = highest level of tetrachloroethylene in air to which a worker may be exposed, averaged over an 8-hour workday.

☐ **NIOSH considers tetrachloroethylene a potential carcinogen and recommends exposure in the workplace be reduced to the lowest possible level.**

The National Institute for Occupational Safety and Health (NIOSH) in 1976 recommended a maximum 8-hour TWA of 50 ppm with a ceiling of 100 ppm, as determined by 15-minute sampling periods. This recommended standard was based on the reported level at which CNS disturbances occurred. In 1978, NIOSH recommended that tetrachloroethylene be handled in the workplace as a potential human carcinogen and that occupational exposure be reduced to the lowest feasible level.

The American Conference of Governmental Industrial Hygienists (ACGIH) has established the following biologic exposure indices (BEIs): 10 ppm tetrachloroethylene in end-exhaled air, sample collected after a minimum of 2 consecutive workdays with exposure; 100 µg/dL tetrachloroethylene in blood, specimen collected after at least 2 consecutive workdays with exposure; and 7 mg/L trichloroacetic acid in urine, specimen collected at end of the workweek. A BEI is a recommended "warning level" and not necessarily a threshold that should not be exceeded. The BEI may be underprotective or overprotective because of individual susceptibility due to the influence of variables such as body habitus, level of activity, and mixed exposures.

Environment

Air

☐ **EPA intends to propose air emission standards for tetrachloroethylene in early 1991.**

EPA intends to propose air emission standards for specific tetrachloroethylene sources in early 1991. These sources will include dry cleaners, chemical manufacturers, and degreasers (solvent cleaning operations).

Water

☐ **EPA has proposed a drinking water maximum contaminant level (MCL) of 5 ppb.**

At present EPA has no standard for tetrachloroethylene in drinking water, but has proposed regulations to take effect in the winter of 1990. The MCL proposed by EPA is 5 ppb; the maximum contaminant level goal (MCLG) proposed is zero.

Challenge

(9) *What authorities should be notified if you believe a product is being used improperly in an industrial setting? By a large number of hobbyists?*

Suggested Reading List

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Environmental Protection Agency. Addendum to the health assessment document for tetrachloroethylene (perchloroethylene), updated carcinogenicity assessment for tetrachloroethylene (perchloroethylene, PERC, PCE). Research Triangle Park, NC: US Environmental Protection Agency, Office of Health and Environmental Assessment, 1986. Report no. EPA/600/8-82/005FA.

Answers to Pretest and Challenge Questions

Pretest

Pretest can be found on page 1.

(a) Your patient is 4 months postpartum, has transient headaches, irritability, decreased ability to concentrate, slightly impaired coordination, and possible alcoholism.

(b) It would help to have more information about the history of her headaches and her silk screening hobby and an accurate history of her current drinking pattern.

(c) Since the patient is postpartum and possibly consumes alcohol in excess, you should rule out anemia and check renal and hepatic functions. A complete blood count, urinalysis, BUN, serum creatinine, and liver function tests would be appropriate.

Challenge

Challenge questions begin on page 3.

(1) The quickest way to identify the ingredients in "Clean Cloth" may be to call your regional poison control center. If this is unsuccessful, ask the patient to obtain a material safety data sheet (MSDS) for "Clean Cloth" from the store that sells it or the manufacturer's sales representative or chemist. (The MSDS will list ingredients in the product and describe their toxicity.)

(2) Yes, maternal exposure to tetrachloroethylene could result in the chemical being transmitted to the nursing infant since the solvent selectively concentrates in breast milk. In addition, the infant may be exposed through inhalation if she is nearby when the fabric is being cleaned.

(3) As is discussed in the Laboratory Tests section, direct indications of tetrachloroethylene exposure can be obtained by measuring levels in breath or blood and by measuring metabolites in urine. Perhaps a first step would be to halt the exposure and determine if the symptoms resolve.

(4) You should inform your patient of the adverse effects of acute and chronic exposure to tetrachloroethylene and advise her and her cousin to use a well-ventilated area when cleaning cloth during silk-screening. You should also review the potential long-term risks, particularly to nursing infants.

(5) Questions about symptoms and temporal association of the use of "Clean Cloth" may reveal a direct connection. The type and amount of ventilation also may have an effect. (Your questioning reveals that the patient sprays the cloth in late afternoon in a small garage and keeps the door closed to prevent dust from entering. She recalls that one day last week when it was hot, she felt particularly ill after spraying the cloth.)

(6) You should review the factors that may reduce the cousin's actual exposure. For example, the cousin may work outdoors or in a better ventilated area, or she may not leave rags soaked with the compound lying about, etc. You could also discuss individual variability as a reason why some people become ill and others do not after similar exposures.

(7) The urinary trichloroacetic acid level indicates an average ambient air exposure of about 30 ppm tetrachloroethylene (calculated using the occupationally based ratio on page 11). While this level indicates definite exposure, it may not be high enough to cause her symptoms; however, the patient could have been periodically exposed to short-term levels much higher than this average level, which could have caused her symptoms.

Although not relevant here, the linear correlation between urinary trichloroacetic acid and tetrachloroethylene exposure levels breaks down when the exposure is above 100 ppm tetrachloroethylene. The plateau effect resulting from saturation of the tetrachloroethylene metabolic pathway limits the effectiveness of the assay when the ambient level is above 100 ppm.

The slightly elevated levels of SGOT and SGPT are inconclusive for tetrachloroethylene exposure because of the confounding factor of alcohol consumption. An SGOT:SGPT ratio greater than 1 (i.e., SGOT greater than SGPT) tends to support an alcoholic etiology; a ratio less than 1 (i.e., SGOT less than SGPT) supports toxic, infectious, or other etiologies. The patient should be advised to reduce alcohol consumption and be counseled regarding alcoholism if this is a problem. Liver function tests should be repeated in several months.

(8) It would be preferable to seek a less toxic replacement. However, if the patient insists on continuing with "Clean Cloth," you should advise her to get proper industrial hygiene consultation or other professional assistance. The local or state health department may be able to provide some information.

Your patient would be well-advised to avoid breast feeding while exposed to tetrachloroethylene. Should she find a "Clean Cloth" alternative that has no chlorinated solvents, the tetrachloroethylene presently in her milk can be eliminated in several days if she continues to pump her breasts.

(9) OSHA has regulatory responsibility for the workplace and should be notified if employees may be dangerously exposed. You could also request that NIOSH initiate a Health Hazard Evaluation of the workplace. A product with hazardous potential used by a number of hobbyists would be reported to the local or state health department.

ATSDR
August 1993
Case Studies in Environmental Medicine

21

Toluene Toxicity

Environmental ALERT . . .

☑ ***Toluene's use is increasing partially because of its popularity as a solvent replacement for benzene.***

☑ ***Gasoline contains 5% to 7% toluene by weight, making toluene a common airborne contaminant in industrialized countries.***

☑ ***Many organic solvents have great addictive potential; toluene is the most commonly abused hydrocarbon solvent, primarily through "glue sniffing."***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. See page 17 for more information about continuing medical education credits and continuing education units.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

A pregnant 28-year-old with cough and dyspnea

A 28-year-old pregnant female comes to your office in the late afternoon with complaints of coughing spasms, chest tightness, and a sensation of being unable to breathe. These symptoms began about 6 hours earlier, while she was repainting a disassembled bicycle with an acrylic lacquer spray paint in a small, poorly ventilated basement area. The painting took about 2 hours to complete.

The patient also experienced nausea, headache, dizziness, and lightheadedness, which cleared within an hour after leaving the basement area. The chest complaints, however, have persisted, prompting the office visit. She is concerned that her symptoms are related to the paint spraying and may affect her pregnancy.

Vital signs include blood pressure 116/80, heart rate 90/minute at rest, respiratory rate 22/minute, and temperature 98.8°F. There are no orthostatic changes in pulse or blood pressure. The HEENT examination is negative except for very mild scleral injection. There are mild expiratory wheezes throughout both lung fields but no rales or no abnormal findings on percussion. Spirometry shows an FEV1 of 72% of predicted value and a moderately decreased peak expiratory flow rate of 275 L/minute. The FEV1/FVC is 75%. Cardiovascular and neurologic examinations are normal. The abdomen is soft and nontender, and a bimanual pelvic examination reveals a 16-week gravid uterus. There is no vaginal bleeding, and no adnexal masses are present.

On questioning the patient further, you discover that 2 years ago she was exposed to fumes of toluene diisocyanate (TDI) from an accidental spill during employment as a bookkeeper at an industrial research laboratory. The patient had only eye and upper airway irritation at the time of the accident but developed severe shortness of breath and coughing 4 hours later. She was hospitalized for several days but recovered.

Pretest

(a) What further information and history would you attempt to elicit?

(b) One of the ingredients in the spray paint is toluene. Could this be responsible for the patient's symptoms?

(c) The patient is concerned about possible effects on the fetus. What advice would you offer?

(d) How will you treat this patient?

Answers can be found on page 15.

Exposure Pathways

☐ **Use of toluene as a benzene replacement is increasing.**

Toluene is a clear, colorless liquid with an aromatic odor. It is a natural constituent of crude oil and is produced from petroleum refining and coke-oven operations. At room temperature, toluene is both volatile and flammable. The odor threshold for toluene in air is low—about 160 parts per billion (ppb), which is about 500 times lower than the level permitted in the workplace. In water, it can be tasted and smelled at a level of 40 ppb. These levels are well below the concentrations at which adverse effects have been observed for short-term exposure. Because toluene is lipid-soluble, it has a moderate tendency to bioaccumulate in the food chain. Synonyms for toluene include toluol, methylbenzene, phenylmethane, and methacide.

☐ **Gasoline, which contains 5% to 7% toluene, is the largest source of toluene release to the atmosphere.**

The principal source of toluene exposure for the general population is gasoline, which contains 5% to 7% toluene by weight. Toluene is released to the atmosphere during the production, transport, and combustion of gasoline. Not surprisingly, toluene concentrations are highest in areas of heavy traffic, near gasoline filling stations, and near refineries. Toluene is short-lived in ambient air because of its reactivity with other air pollutants.

☐ **Common household products and cigarette smoke contribute to toluene in indoor air.**

Common household products and cigarette smoke are the principal sources of toluene indoors. Indoor air is often several times higher in toluene concentration than outside air. Cigarette smokers absorb about 80 to 100 micrograms (µg) of toluene per cigarette. Toluene-containing consumer products include household aerosols, paints, paint thinners, varnishes, shellac, rust inhibitors, adhesives and adhesive products, and solvent-based cleaning and sanitizing agents. Toluene is used as a solvent in cosmetic nail polishes at concentrations up to 50%.

Industrial use of toluene as a solvent replacement for the more toxic benzene is increasing. In addition to the products mentioned above, toluene is commonly used in some printing operations, leather tanning, and chemical processes.

Intentional inhalation of toluene makes it one of the most abused hydrocarbon solvents. Glues, paints, and solvent mixtures are the most commonly abused products.

Although most environmental toluene is released directly to the atmosphere, it is occasionally detected in drinking-water supplies. Water contamination occurs because toluene is a common chemical in hazardous waste and sludge disposal sites, industrial effluents, and petroleum wastes. Nonetheless, drinking water levels of toluene are usually low relative to those of other volatile organic chemicals.

Challenge

Additional information for the case study: The patient brings you the spray paint can, which lists the following ingredients on the label: paint (pigment), petroleum distillates, and a minor amount of methanol. A call to the regional poison control center reveals that the petroleum spirits in this brand of paint are mostly toluene, with minor amounts of xylene. The patient asks you if this toluene is the same chemical that caused her hospitalization 2 years ago.

(1) How will you answer the patient's question?

Who's at Risk

Workers who manufacture or use toluene or toluene-containing products are at increased risk of exposure. An estimated 4 to 5 million workers are occupationally exposed to toluene. Automobile mechanics; gasoline manufacturers, shippers, and retailers; dye and ink makers; and painters are at greatest risk. Other workers who are potentially exposed to toluene include, but are not limited to, the following:

adhesives and coatings manufacturers and applicators
chemical industry workers
coke-oven workers
fabric manufacturers (fabric coating)
hazardous waste site personnel
linoleum manufacturers
pharmaceutical manufacturers
shoe manufacturers
styrene producers

Many organic solvents, including toluene, have an addictive potential equal to that of alcohol or opiates. The adolescent population is most likely to intentionally abuse solvents, although the prevalence of this abuse is unknown. Solvent inhalation techniques are referred to as "bagging" or "huffing." Studies indicate that volatile-solvent sniffers are typically boys between the ages of 10 and 15 years of age who concurrently use or later develop an alcohol, marijuana, or opiate habit. In general, solvent abuse tends to decrease with increasing age, but adults of both sexes are known to abuse organic solvents.

☐ **Chronic, intentional toluene abuse may lead to serious adverse effects and death.**

☐ **Concurrent use of alcohol or salicylates increases the risk of adverse effects from toluene exposure.**

☐ **Persons with cardiovascular, respiratory, and liver disease are at increased risk of toluene's adverse effects.**

Because toluene is metabolized in the liver, liver disease may increase its acute toxic effects. Concurrent use of alcohol, which competitively inhibits toluene metabolism, may also increase toluene's acute effects. In addition, experimental animal studies indicate that chronic exposure to toluene augments alcohol-induced fatty liver disease; thus, workers exposed to toluene who are chronic alcohol drinkers may have added risk due to their inability to detoxify alcohol. Because salicylates can also competitively inhibit toluene metabolism, concurrent use of salicylates may reduce the clearance of both toluene and salicylates.

Like many organic solvents, toluene is a respiratory-tract irritant, particularly at high airborne concentrations. Persons with underlying respiratory-tract disorders, such as asthma and chronic obstructive pulmonary disease (COPD) or reactive airways dysfunction syndrome (RADS), may experience bronchospasm on exposure to any irritant, including toluene.

Because toluene accumulates in adipose tissues, obese persons tend to retain more toluene than persons of normal weight, but the clinical significance of this is unknown.

Challenge

Additional information for the case study: The patient's history is negative for asthma, chronic bronchitis, and allergic conditions. She has not been employed in any position entailing chemical exposure since the toluene diisocyanate exposure 2 years ago, but she has noticed mild, transient chest tightness and difficulty breathing when using self-service gasoline filling stations and when exposed to tobacco smoke.

(2) Could the patient's current problem be related to the spray paint? Explain.

Biologic Fate

Inhalation is the primary route of toluene exposure, but significant amounts can be absorbed through ingestion and dermal contact. Peak blood concentrations occur 15 to 30 minutes after inhalation. The amount of toluene absorbed by inhalation depends on the respiratory minute volume; thus, exercise affects the absorption rate of toluene. At rest, the lungs absorb about 50% of an inhaled dose.

☐ **Systemic absorption of inhaled toluene is rapid.**

The rate of absorption after oral intake is slower than after inhalation. Nevertheless, gastrointestinal absorption is nearly complete and blood toluene levels peak 1 to 2 hours after ingestion. Percutaneous absorption is slow through intact skin and rarely produces toxicity.

☐ **Toluene is distributed to highly perfused and fatty tissues.**

Toluene is lipophilic and has little water solubility. It is distributed quickly to highly perfused tissues such as brain, liver, and kidney. It passes readily through cellular membranes and accumulates primarily in adipose and other tissues with high fat content. In the body, the half-life of toluene ranges from several minutes in highly vascular organs to slightly over one hour in fatty tissue. Toluene's affinity for the lipid-rich structures of nervous tissue results in central nervous system toxic effects within minutes.

☐ **The major toluene metabolite is hippuric acid, which is excreted in the urine.**

About 80% of absorbed toluene is oxidized in the liver to benzoic acid, which is then conjugated with glycine to form hippuric acid or with glucuronic acid to form benzoyl glucuronate. A small amount of toluene undergoes aromatic ring oxidation to form ortho- and para-cresols. Most inhaled or ingested toluene is eliminated in urine within 12 hours after exposure; a small amount (up to 20%) is eliminated as free toluene in expired air. Less than 2% of total toluene metabolites are excreted in the bile.

Challenge

(3) Is there any clinical benefit in measuring blood toluene levels or levels of urinary toluene metabolites in this patient?

Physiologic Effects

Central Nervous System Effects

☐ **The principal effect of toluene exposure is central nervous system depression.**

Toluene produces reversible effects on the liver, kidneys, and nervous system; the nervous system appears to be most sensitive to its effects. The physiologic effects of toluene depend on the concentration and length of exposure. Most data concerning toluene's effects on human health come from studies of workers with chronic exposure to toluene or from intentional solvent abusers who inhale high levels of toluene for self-intoxication. The applicability of this data to relatively low-level exposure in the environmental setting, however, is unknown.

Toluene's anesthetic action can result in rapid central nervous system (CNS) depression and narcosis at high concentrations. Volatilization after ingestion and hypoxia after aspiration can contribute to CNS toxicity, and aromatic impurities in commercial toluene-containing products may have added neurotoxic effects.

At low concentrations, toluene produces disturbances in basal ganglia dopaminergic mechanisms in experimental animals. Human exposure to 100 parts per million (ppm) of toluene (the permissible exposure level in the workplace) caused substantial complaints about poor air quality, altered temperature and noise perception, increased irritation of the nose and lower airways, and feelings of intoxication. Chronically exposed workers have scored lower on some tests of cognitive performance than unexposed controls.

Several studies have examined the neuropsychiatric effects of acute exposure to toluene vapors. Cerebellar and CNS integrative dysfunction predominate. In addition, peripheral nerve dysfunction has been reported, but the peripheral neuropathies may have been due to impurities, such as n-hexane, in the toluene. Long-term toluene abuse has led to neuropsychiatric and neurobehavioral disorders, which in many cases, but not all, were reversible. Some chronic toluene abusers have developed structural CNS damage.

Respiratory Effects

☐ **Toluene is a respiratory-tract irritant.**

Toluene acts initially as a respiratory-tract irritant. Several mechanisms precede respiratory decompensation: replacement of alveolar air by vaporized hydrocarbon, ventilation-perfusion dysfunction caused by bronchospasm, formation of a hyaline membrane, and solubilization of the lipid surfactant layer. As severity of exposure increases, respiratory depression leading to death can result.

Pulmonary aspiration of gastric contents that may occur during altered consciousness can lead to chemical pneumonitis.

Cardiac Effects

Toluene appears to lower the threshold of myocardial susceptibility to the dysrhythmic effects of catecholamines. Sudden death among volatile-solvent abusers has often been preceded by strenuous physical activity and is believed to result from lethal, nonperfusing cardiac dysrythmias. In cases of severe poisoning, cardiac dysrythmias may also occur secondary to hypoxia and acidosis caused by CNS-mediated hypoventilation.

☐ **Cardiac dysrhythmias are postulated as a leading cause of death after intentional toluene abuse.**

Hematopoietic Effects

Toluene does not cause the hematopoietic effects noted with chronic benzene exposure. Early studies suggesting such effects were performed with toluene that was contaminated with benzene. Modern distillation methods prevent significant benzene contamination of toluene.

☐ **Toluene does not cause the severe blood dyscrasias associated with benzene exposure.**

Other Effects

Metabolic acidosis, hypokalemia, hematuria, proteinuria, distal renal-tubular acidosis, and pyuria have been reported in chronic volatile-solvent abusers, although these effects usually have been reversible. Accumulation of hippuric acid and other organic acid byproducts of toluene metabolism is thought to be responsible for the elevated anion-gap metabolic acidosis that occurs with toluene abuse. Elevated urinary concentration of retinol-binding protein has been correlated with toluene exposure in a dose-dependent manner, which suggests that early renal-tubular effects may occur in abusers. Hepatotoxicity has been reported in glue sniffers, but studies in chronically exposed workers show no or minimal hepatic damage.

☐ **Metabolic acidosis can occur in persons who abuse volatile solvents, including toluene.**

Toluene has been implicated in adverse developmental effects that have occurred in offspring of chronic toluene abusers. Children chronically exposed in utero from high-dose maternal solvent abuse throughout pregnancy have demonstrated microcephaly, CNS dysfunction, attention deficits and hyperactivity, developmental delay, minor craniofacial and limb anomalies, and variable growth deficiency. Severe neonatal acidosis has also been noted, possibly secondary to maternal renal-tubular acidosis. However, these case reports must be regarded with caution because all results to date have been confounded by probable exposure to alcohol or other organic solvents during pregnancy. In addition, the small number of exposed persons and the lack of precise exposure data limit the conclusions that can be drawn.

☐ **The role of toluene in developmental toxicity is uncertain.**

☐ **Toluene is not considered a human carcinogen.**

Although epidemiologic studies of workers exposed to multiple organic solvents have found greater risks of death from numerous cancers compared to the general nonexposed population, there is no evidence that toluene alone causes cancer. Animal studies have not suggested that toluene is carcinogenic.

In high concentrations, toluene exerts an irritant action on the eyes, skin, and mucous membranes. Direct dermal exposure defats the skin, leading to dryness, fissuring, and possible secondary infection. A few cases of contact urticaria have been described after occupational exposure to a solvent mixture containing toluene, but it is not clear that toluene was the responsible agent.

Challenge

(4) The patient expresses concern that her fetus may have been harmed by the exposure to toluene in the spray paint. What advice can you give her?

(5) Should the patient be concerned about future development of cancer from the spray paint exposure?

Clinical Evaluation

History and Physical Examination

Because signs and symptoms of toluene intoxication typically depend on the intensity and duration of exposure, assessment of a patient with suspected toluene exposure begins with defining the route(s) of exposure and determining if the exposure was acute or chronic and at what concentrations. The temporal relationship of symptom onset to possible exposure should be explored. In addition, the following information may be helpful: occupational history; recent hobbies and household remodeling projects, particularly painting and furniture refinishing; use of consumer products such as nail polish, adhesives, aerosols, and solvent-based cleaners. Because many products containing toluene are mixtures, attempts should be made to ascertain the total composition. Proximity of residence to landfills and industrial facilities and the source of drinking water may provide clues to environmental exposures. (See *Case Studies in Environmental Medicine: Taking an Exposure History*.)

Clinical evaluation of a patient with acute exposure should focus on organ systems most often affected by toluene: neuropsychiatric, renal, cardiovascular, and respiratory. In the case of chronic abusers, the hepatic system should also be evaluated. Possible volatile-solvent abuse and concomitant use of alcohol or other drugs of abuse should be considered when chemically induced CNS depression is present.

Signs and Symptoms

Acute Exposure

Substantial nonoccupational, acute exposures to toluene are most frequently the result of intentional inhalation of glue, paint, or solvent vapors. High-concentration exposures may also occur in hobbyists and do-it-yourself workers in confined spaces. Acute exposure results in CNS depression with headache, dizziness, lightheadedness, and euphoria and can lead to cardiopulmonary collapse, coma, and death.

☐ **Symptoms are unlikely to occur after exposure to airborne concentrations below the odor threshold.**

In addition to CNS depression, acute ingestion can cause nausea, vomiting, possible hematemesis, and burning of the oropharynx and epigastrium. Aspiration can lead to hoarseness, coughing, and chemical pneumonitis.

If a large ingestion of toluene is suspected or if respiratory distress develops after acute inhalation exposure, hospital admission, chest radiography, spirometry, determination of arterial blood gases, and monitoring of vital signs are recommended. Acutely exposed patients who are asymptomatic and have a negative chest X ray do not require further hospital observation.

Dermal exposure usually causes skin irritation only. When contact with the solvent is unusually extensive and prolonged, some systemic absorption may occur. Ocular exposure to liquid toluene may cause corneal burns.

Chronic Exposure

☐ **Chronic solvent abuse is associated with various neurobehavioral and neuropsychologic effects.**

Repeated high-dose exposures associated with solvent abuse may result in progressive memory loss, fatigue, poor concentration, irritability, persistent headaches, and signs and symptoms of cerebellar dysfunction. Although these effects generally are reversible if exposure ceases, some patients remain substantially impaired. Muscular weakness has been noted in patients who develop renal-tubular acidosis.

Laboratory Tests

If toluene exposure is suspected, baseline studies should include the following:

electrolytes
BUN and creatinine
liver enzymes
urinalysis
electrocardiogram with rhythm monitoring

Repeat baseline tests in 3 to 6 months to detect delayed hepatic, renal, or neuropsychiatric effects. Patients with substantial chronic exposures should have annual assessments. Referral for detailed neuropsychologic assessment is indicated only if the patient's abnormal mental status or behavioral changes persist after exposure ceases.

Direct Biologic Indicators

☐ **Toluene can be measured in blood, but the level has little clinical relevance.**

Because excretion of toluene and its metabolites is rapid (essentially complete within 12 to 24 hours), biologic samples for analysis must be obtained soon after exposure. A venous blood sample taken within a day after exposure can be used to confirm toluene exposure (normal for unexposed populations is 0.1 milligrams/deciliter [mg/dL]); however, the toluene level obtained will not correlate well to the degree of exposure or to symptoms. Analysis of exhaled air for toluene is experimental only.

Indirect Biologic Indicators

☐ **Urinary hippuric acid levels should be interpreted with caution.**

Hippuric acid, a metabolite of toluene, may also result from the metabolism of other chemicals, including common food additives, and is typically found in significant amounts in the urine from unexposed persons. Hippuric acid levels higher than 2.5 grams per gram (g/g) creatinine suggest toluene exposure.

Treatment and Management

Acute Exposure

There is no antidote for toluene intoxication; care is supportive. In cases of acute exposure, treatment consists of removal of patients from the contaminated environment, support of cardiopulmonary function, and prevention of further absorption. Patients with inhalation exposure may require low-flow oxygen (approximately 40%) and hydration. More severe cases may require assisted ventilation. Contaminated clothes should be removed and isolated, decontaminated, or disposed of safely. Exposed skin should be washed thoroughly with soap and water. Treatment of ocular exposure should begin with irrigation for at least 15 minutes.

☐ **There is no antidote for toluene toxicity.**

In cases of toluene ingestion, do not induce emesis because of the risk of CNS depression and subsequent pulmonary aspiration from vomiting. Standard regimes for administering a cathartic and activated charcoal should be followed. If the patient has ingested a large amount (greater than 5 milliter [mL]) of toluene and is examined within 30 minutes of ingestion, the benefits of gastric lavage should be weighed against the risk of pulmonary aspiration. Ingestion of a small amount (5 mL or less) of toluene may be treated by administering activated charcoal orally without emptying the gut.

☐ **Therapy for toluene overexposure consists of supportive care.**

Epinephrine and other catecholamines should be used cautiously because of risk of cardiac dysrhythmias. In substantial intoxications, fluid and electrolytes should be monitored. Intravenous potassium and sodium bicarbonate may be required to correct hypokalemia and acidemia, respectively. Hypocalcemia may be corrected with intravenous calcium. Use appropriate supportive treatment to correct acute renal failure if it occurs.

Discharge planning should include follow-up of hepatic, renal, and neuropsychiatric status and referral for substance-abuse treatment when appropriate. Environmental conditions that may have led to unintentional exposures should be corrected.

Chronic Exposure

There is no specific clinical treatment for patients who have been chronically exposed to toluene. Sources of exposure must be identified and minimized. Intentional volatile-solvent abusers should be referred to appropriate treatment programs to encourage abstinence.

☐ **There is no clinical treatment for chronic toluene exposure.**

Challenge

(6) How will you treat the patient in the case study?

Standards and Regulations

Workplace

Air

The workplace air standards mandated by the Occupational Safety and Health Administration (OSHA) include an 8-hour time-weighted average (TWA) of 100 ppm and a short-term exposure limit (STEL) of 150 ppm. The National Institute for Occupational Safety and Health (NIOSH) recommends a TWA of 100 ppm and a STEL of 150 ppm. NIOSH has established the level of 2000 ppm as immediately dangerous to life or health (IDLH). The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a threshold limit value (TLV) identical to the OSHA standards (Table 1).

Environment

Air

The federal government has not established specific standards for toluene in ambient air. At least 10 states have guidelines or standards for acceptable ambient air concentrations of toluene.

Water

As of July 30, 1992, the Environmental Protection Agency (EPA) has instituted a maximum contaminant level (MCL) of 1 ppm (1.0 milligrams per liter [mg/L]) for toluene in drinking water. Approximately 10 states have drinking water standards or guidelines for toluene ranging from 0.1 to 2 ppm.

Table 1. Standards and regulations for toluene

Agency[*]	Focus	Level	Comments
ACGIH	Air-workplace	100 ppm (375 mg/m^3) 150 ppm (560 mg/m^3)	Advisory; TLV-TWA[†] STEL[‡]
NIOSH	Air-workplace	100 ppm (375 mg/m^3) 150 ppm (560 mg/m^3)	Advisory; TWA STEL
OSHA	Air-workplace	100 ppm (375 mg/m^3) 150 ppm (560 mg/m^3)	Regulation; PEL[§] as TWA STEL
EPA	Drinking Water	1 ppm (1.0 mg/L)	Regulation; MCL[**]
			Health Advisories
		21.5 ppm (21.5 mg/L)	1 day
		3.46 ppm (3.46 mg/L)	10 day
			Longer term
		3.46 ppm (3.46 mg/L)	Child
		2.42 ppm (2.42 mg/L)	Lifetime

[*] ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration

[†] TLV-TWA (threshold limit value—time-weighted average) = time-weighted average concentration for a normal workday and a 40-hour workweek to which nearly all workers may be repeatedly exposed.

[‡] STEL (short-term exposure limit) = maximum level allowed in any 15-minute sampling period.

[§] PEL (permissible exposure limit) = highest level in air to which a worker may be exposed, averaged over an 8-hour workday.

[**] MCL (maximum contaminant level) = enforceable level for drinking water.

Biologic Standards

Biological exposure indices (BEI) are reference values established by ACGIH that are intended as guidelines for evaluating potential exposure hazards in the workplace. The BEI for the urinary metabolite of toluene (hippuric acid) is 2.5 g/g creatinine; the sample is collected at the end of the work shift. Hippuric acid is also a metabolite of other aromatic solvents and certain endogenous agents; therefore, it is not specific to toluene. The BEI for toluene in venous blood, collected at the end of the work shift, is 1.0 mg/L; whereas the toluene index in end-exhaled air (the residual air in the lungs after the person has exhaled normally), measured during the work shift, is 20 ppm. These biologic standards are useful as confirmatory tests for the effectiveness of workplace industrial hygiene practices but not for comparison in cases of acute exposure.

Suggested Reading List

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Government Documents

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Sources of Information

More information on the adverse effects of toluene and treating and managing cases of exposure to toluene can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Toluene Toxicity* is one in a series. For other publications in this series, please use the order form on the inside back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of the Director, at (404) 639-6204.

Answers to Pretest and Challenge Questions

Pretest questions are found on page 1. Challenge questions begin on page 3.

Pretest

(a) The ingredients of the spray paint should be identified. Obtaining the original container and inspecting the label may be sufficient. If the ingredients are not listed on the label, the information may be obtained by contacting the distributor or manufacturer, or the information may be available from the regional poison control center.

Further history should include questions regarding previous bouts of asthma, chronic bronchitis, allergic conditions, and prior episodes of chest complaints after chemical exposure.

(b) Yes. The patient's transient nausea, headache, dizziness, and lightheadedness are consistent with exposure to toluene (but not with exposure to toluene diisocyanate). Although toluene can be irritating to the airways, the degree of wheezing and dyspnea experienced by this patient and the persistence for several hours after exposure has ceased both indicate that an intercurrent disorder may be present.

The patient has no history of chronic respiratory disease, yet pulmonary function testing suggests airway obstruction. She has had a previous significant exposure to a strong respiratory-tract irritant (toluene diisocyanate), which caused severe respiratory symptoms within 24 hours; she reports that since then exposure to irritating substances continues to provoke symptoms similar to asthma. This history suggests reactive airways dysfunction syndrome, or RADS. (See below for criteria used to diagnose RADS.) Using the spray paint in a poorly ventilated room could readily create a toluene concentration irritating enough to provoke bronchospasm in a patient with RADS.

The diagnostic criteria for RADS include the following:
- no history of respiratory system complaints
- a single, specific exposure in an accident or incident involving high concentrations of an irritant fume, gas, or vapor that was associated with the initial symptoms
- symptoms onset occurred within 24 hours of the initial exposure and persisted for at least 3 months
- pulmonary function tests usually indicate airflow obstruction challenge testing is positive
- other types of pulmonary disease have been ruled out

(c) Toluene has caused fetal malformations in chronically exposed experimental animals. Cases have been reported of congenital malformations and severe neonatal acidosis in infants of women who chronically abused toluene throughout pregnancy. In most of those cases, the toluene doses were very high, and concomitant abuse of ethanol occurred so that fetal alcohol syndrome cannot be excluded. Given the mild, brief exposure that this patient incurred, it is unlikely that the fetus was harmed. Should the patient desire further counseling, you could refer her to a teratology consulting service such as the Motherisk Program at the Hospital for Sick Children in Toronto, (416) 598-5781.

(d) Treatment for RADS is essentially the same as treatment for asthma: ß-agonist inhalants (e.g., albuterol or terbutaline sulfate), cromolyn sodium, and corticosteroids. Of the various ß-agonist inhalants, terbutaline sulfate is not teratogenic in experimental animals and may represent the best choice for this patient. Consider cromolyn sodium if prophylactic treatment is deemed necessary. The usual precautions for use of corticosteroids apply. The patient should be counseled to avoid exposure to all pulmonary irritants.

Challenge

(1) You could explain to the patient that toluene diisocyanate (TDI) is not the same chemical as the chemical in the spray paint. Both toluene and toluene diisocyanate are liquids, but their chemical structures are different, as are their toxicities. Toluene is a common solvent found in many household products; its toxicity is low, and at low doses (less than 100 ppm) it normally causes few symptoms. On the other hand, TDI is very irritating to the eyes and respiratory tract and may cause bronchospasm at levels less than 1 ppm. Furthermore, TDI can sensitize exposed individuals and cause coughing spasms at even lower levels than the original exposure, and this does not occur with toluene.

(2) See (b) above.

(3) There is little clinical benefit in measuring blood toluene levels or levels of toluene metabolites such as hippuric acid in the urine. Treatment would not be altered regardless of the results. The only available comparison data are from either deliberate toluene abusers or asymptomatic workers with chronic exposure, and it is unclear how such data would apply to this patient.

(4) See (c) above.

(5) There are few data to suggest that toluene is carcinogenic. Earlier incidents of cancer occurring after chronic toluene exposure were caused by toluene's significant contamination with benzene, which is a known carcinogen. (Benzene is no longer a contaminant of toluene.) The patient can be reassured that a single exposure to toluene is unlikely to cause or contribute to the development of cancer.

(6) See (d) above.

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Occupational Asthma Due to Toluene Diisocyanate Among Velcro-Like Tape Manufacturers

Jung-Der Wang, MD, ScD, Ping-Hung Huang, MD, Jia-Ming Lin, PhD, Shyh-Young Su, BS, and Min-Chien Wu, MD

During September-November, 1985, four employees of a factory were seen at the occupational clinic complaining of cough, shortness of breath, and wheezing. All four worked in the same area of the factory where an adhesive containing toluene diisocyanate (TDI) was applied to velcro-like tape during manufacturing. To confirm the diagnosis of TDI-induced asthma and determine the prevalence among workers, 38 workers were interviewed and examined (84%) in the factory. Air samples were also taken from several areas in the factory to determine the TDI concentration. For analysis, the factory was divided into three areas based on the concentration of TDI: low (0.012 ± 0.002 ppm), medium (0.021 ± 0.006 ppm), and high (0.047 ± 0.054 ppm). The distribution of workers with symptoms of asthmatic bronchitis was highly associated with TDI concentration ($p < 0.001$). After stopping work for a period of 10 days, workers in areas with a high concentration of TDI showed marked improvement in pulmonary function tests (PFTs). After isolation of the exposure site, improvement of the ventilation system, and substitution of the TDI with less volatile diphenylmethane diisocyanate (MDI), air concentration of isocyanates was usually below 0.007 ppm. Three of the four clinically overt asthma cases went back to work without any difficulty. The PFTs of affected workers showed a significant improvement 5 months later. We conclude that TDI was responsible for the occupational asthma among velcro-like tape manufacturers and that the TDI-induced impairment of pulmonary functions was at least partially reversible.

Key words: TDI, asthma, isocyanates, MDI

INTRODUCTION

During September-November, 1985, four employees of a factory in Taipei County were seen in an outpatient clinic of the National Taiwan University Hospital complaining of cough, shortness of breath, chest tightness, and wheezing. The symptoms tended to be worse at night and improved after long holidays. All four employees worked in the same area in the factory where an adhesive was applied to the velcro-like tape during the manufacturing process. A review of all the processes

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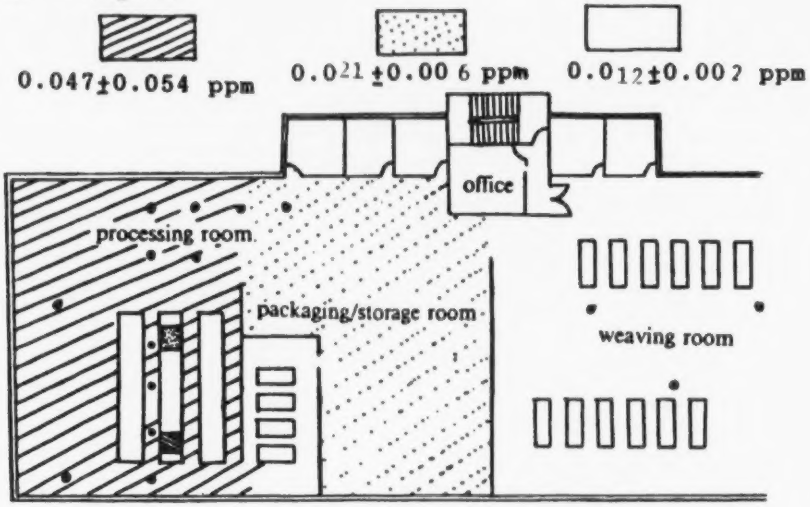

Fig. 1. Floor plan and distribution of TDI concentration in air samples of the velcro tape manufacturing factory. Big black dots indicate the place where samples were taken. ▨ indicates the place where the adhesive is applied to the tape; □ indicates the place where the adhesive is heated and dried.

found that the adhesive resin contained toluene diisocyanate (TDI), a well-known cause of occupational asthma [NIOSH, 1978; Chan-Yeung and Lam, 1986; NIOSH, 1977b]. Because TDI-induced occupational asthma has never, to our knowledge, been documented in Taiwan, this study was conducted to determine the etiology and prevalence rate of this outbreak of workers' asthma.

MATERIALS AND METHODS

The factory has 45 employees and has been in operation since 1984. Most of the employees were young women (median age 22 years). The female to male ratio was 3.2:1. The employees' turnover rate was high; the average length of employment was 9.2 months. We tried to interview and examine all employees. Air samples were taken by midget impingers at different locations in the factory and they analyzed for TDI concentrations by colorimetric methods [NIOSH, 1977a]. Pulmonary function tests (PFTs) [Ferris, 1978] were also performed on workers, using a portable spirometer (Chest autospiror-298), during a usual workday, after a 10-day holiday, and 5 months after the improvement of the workplace by effective isolation and ventilation control. All tests were done in the morning (between 8:30–10:30 AM) at the factory office to avoid across-shift functional deterioration.

The factory was divided into three functional areas: the weaving area, where the tape is woven; the processing area, where the tape is dyed and the adhesive resin is applied; and the packaging/storage area. The three areas were connected through doors, with the packaging area in the middle of the other two (Fig. 1).

A case of asthma or asthmatic bronchitis was defined as any worker who

TABLE I. Incidence of Asthmatic Bronchitis Symptoms by Workplace and Air Concentration of Toluene Diisocyanate (TDI)*

Workplace	Air concentration of TDI (in ppm)	Case	Non-case	Total	Rate (%)
Processing	0.047 ± 0.054	11	2	13	84.6
Packaging/ Storage	0.021 ± 0.006	3	5	8	37.5
Weaving	0.012 ± 0.002	0	13	13	0.0
Total		14	20	34	41.2

*X^2 Mantel-test for trend = 18.6 ($p < .001$)

developed symptoms of cough for more than 1 month and shortness of breath or wheezing for 1 month after working in this factory. Workers with a history of prior cardiovascular or pulmonary diseases, previous known exposure to pulmonary irritants, and previous smoking history were excluded from analysis.

Mantel extension for the test of trend [Mantel, 1963] and paired Student's t-test were performed to evaluate the statistical significance.

RESULTS

Completed interviews and physical examinations were obtained for 38 of 45 (84%) workers; of these, four workers were excluded because of a smoking history. Among the remaining 34 workers, 14 met the case definition for asthma or asthmatic bronchitis. The highest attack rate occurred among workers in the tape processing area and the lowest was in the weaving area. Four of 14 cases of asthma compared with none of the noncases had wheezing rales on chest examination ($p<0.0001$). All four cases with auscultatory findings worked in the tape processing area.

Air samples collected from various locations in the factory revealed that TDI concentrations were highest in the tape processing area with a mean of 0.047 ± 0.054 ppm ($n = 15$), and lowest in the weaving area with a mean of 0.012 ± 0.002 ppm ($n = 3$). The packaging/storage area had intermediate levels of TDI with a mean of 0.021 ± 0.006 ppm ($n = 3$). A highly significant trend was noted between the increased concentration of TDI and the increased occurrence rate of asthma (Table I).

Since some workers left the company after the 10-day holiday, we successfully performed pulmonary function tests before and after holiday on only 21 workers, at the factory office between 8:30–10:00 AM before the start of work. Workers in the processing area had the greatest changes in pre- and post exposure FEV_1 and FVC (Table II).

Based on the results of the investigation, we recommended that the factory install new ventilation hoods, improve the design of existing hoods, and isolate the process of applying TDI-containing adhesives to protect workers from TDI vapors. We also recommended the factory change the formula of the adhesive resin and substitute diphenyl methane diisocyanate (MDI) for TDI, because MDI has a higher vaporization temperature and a lower vaporization pressure [ACGIH, 1980]. Five months after these recommendations were implemented, workers were reexamined and air samplings were repeated. No worker complained of asthmalike symptoms. FEV_1 and FVC measurements for 10 workers still employed at the time of follow-up

TABLE II. Change in Pre- and Postexposure One-second Forced Expiratory Volume (FEV) and Forced Vital Capacity (FVC) Among Employees Classified by Workplace

Workplace	No. workers	Change in FEV (mean ± 1 S.D., in ml)		Change in FVC (mean ± 1 S.D., in ml)		p-value*
Processing	9	−431 ± 246		−334 ± 279		
			p = 0.035		p = N.S.	
Packaging/storage	4	−118 ± 102		−146 ± 123		p < 0.005
			p = N.S.		p = N.S.	
Weaving	8	+10 ± 311		+36 ± 145		

*Student's t-test, N.S. = not significant.

showed significant improvement in pulmonary function (Table III). The mean duration of employment of these workers before our examination was 7.7 ± 4.6 months. Seven of 9 air samples showed undetectable concentrations of isocyanates; the other two samples were below 0.007 ppm at the processing area.

DISCUSSION

Diisocyanates are used quite extensively in many industries for manufacturing polyurethane resins of various physical properties, e.g., hard, flexible, or semirigid foams. They may cause irritation of eyes, respiratory tract, and skin. The irritation may be severe enough to produce bronchitis and pulmonary edema. It has been estimated that approximately 4.3–25% of workers exposed to an air level of .02 ppm TDI develop asthma. [Weill et al., 1981; Adams, 1975] Symptoms may develop weeks or months after exposure. Exposure to very low levels of TDI (<.005 ppm) may induce an asthmatic attack in individuals sensitized by previous exposure to TDI. Therefore, an IgE-mediated allergic mechanism has been postulated but not unequivocally confirmed as the cause of TDI-induced asthma [Chan-Yeung and Lam, 1986]. Another possible mechanism is through a pharmacologic reaction of the bronchus. In either case, the establishment of diagnosis may be through a bronchial provocation test [Pepys and Hutchcroft, 1975] or an epidemiological study. Because an epidemiologic approach can directly examine the workplace, we took this method and performed air measurements of TDI. The current threshold limit value (TLV) recommended by the American Conference of Governmental Industrial Hygienists is 0.005 ppm [ACGIH, 1986]. All 11 air samples originally taken in the processing area were above this level. The highest concentration measured, at the drying operation (Fig. 1), was 0.236 ppm, which was more than 47 times the TLV. The higher attack rates of asthmalike symptoms reported in our investigation may have been due to the difficulty in distinguishing true allergic cases from workers with other symptoms of pharmacologic reaction or pulmonary irritation, e.g., bronchitis, following exposure to high levels of TDI. We were able to show an objective reduction in pulmonary function for workers in areas with occasional high TDI concentrations. Both symptoms and pulmonary function tests improved after a period (10 days) away from the factory and also after improvements were made in the factory's design and ventilation system. In fact, three of the four workers with clinically overt asthma went back to work without any symptoms. The fourth worker has not gone back to the factory, although she is currently asymptomatic and her lung function has returned to

TABLE III. Improvement in Pulmonary Function Tests Among Employees Under Different Working Conditions*

	Beginning of study (ml)	After 10-day holiday (ml)	5 months after recommendations (ml)
FEV_1 (mean ± 1 S.D.)	1978 ± 588	2250 ± 342	2422 ± 377
		p = 0.048	p = 0.004
FVC (mean ± 1 S.D.)	2605 ± 366	2799 ± 276	3025 ± 347
		p = 0.004	p = 0.002

*p-values calculated using paired Student's t-test.

within normal. Therefore, we concluded that both asthma and other symptoms of pulmonary irritation were due to occupational exposure to TDI, and that the improvement in the work environment was effective.

Although some authors have reported that ventilatory functions may not fully recover among all sensitized workers after removal from TDI exposure [Adams, 1975; Weill et al., 1981], we did find a significant improvement of lung function among workers. Possible explanations for the discrepancy of these findings are: 1) many of our workers with symptoms of occupational asthma may not have been truly sensitized and developed symptoms simply because of the irritant effect of TDI; 2) our 10 workers had shorter durations of exposure to TDI, i.e., 7.7 ± 4.6 months, which might only cause a more reversible effect.

This investigation clearly illustrates the impact of an occupational health hazard in a factory. The prevalence of occupational diseases in Taiwan is unknown but is probably high given the rapid industrialization and increased use of many potentially hazardous chemicals in manufacturing in recent years. At present, governmental agencies responsible for monitoring occupational diseases are grossly underfunded and understaffed. This investigation illustrates not only that occupational health problems exist in Taiwan, but they can often be remedied with minimal cost to industry. The key to improving occupational health among workers in Taiwan and elsewhere is to establish better procedures for licensing and inspecting factories and to train physicians and industrial hygienists to conduct proper health hazard evaluations and implement environmental control measures.

ACKNOWLEDGMENTS

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ATSDR September 1993
Case Studies in Environmental Medicine

24

1,1,1-Trichloroethane

Environmental ALERT . . .

☑ ***Although 1,1,1-trichloroethane will be phased out of use by 1996, it will remain an environmental concern. Its wide use as a solvent in industry and for consumer products has resulted in large amounts being released to the environment. In addition, about 20% of the approximately 1200 hazardous waste sites on the National Priorities List contain this chemical.***

☑ ***For the general population, the most likely sources of exposure to 1,1,1-trichloroethane are home consumer products, building products, and contaminated food and water.***

☑ ***Inhalation abuse of 1,1,1-trichloroethane can result in "sudden sniffing death."***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. See page 17 for more information about continuing medical education credits and continuing education units.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

A mother who attributes her daughter's congenital heart defect to air pollution

Your practice is located in a valley with a number of computer-related, high-technology, "smokeless" industries. One of your patients, a young mother whose 8-month-old daughter was born with a congenital heart defect, comes to your office to discuss a recent newspaper article that suggests toxic chemicals may cause birth defects. After reading the article, she discovered that two of her neighbors had miscarriages shortly before her daughter's birth, two neighbors had recently given birth to babies who have defects, and one neighbor had a stillbirth. Many of the neighbors spoke of often-smelling a sweet, solvent-like odor in the outdoor air.

Your patient is determined to confirm her suspicion that a chemical in the air from the local computer chip manufacturing plant is responsible for these events. She has called the city council and is not satisfied that she will get a prompt hearing. She has organized a small group of concerned citizens. She asks you to be a consultant to the group and provide medical information at the group's first meeting.

Your patient gives you a list of chemicals that she has determined are or have been used at the plant. The list includes arsine, phosphine, trichloroethylene, 1,1,1-trichloroethane, tetrachloroethylene, epoxy resins and curing agents, hydrofluoric acid, and gallium arsenide. You know that arsine, phosphine, and hydrofluoric acid are quite toxic and used in relatively small quantities in the electronics industry. Emissions are unlikely to escape the plant daily. In addition, the odors of these chemicals do not fit the patient's description. The epoxy resins and gallium arsenide are not volatile substances and are not likely to be detected outside the plant. You conclude that the chemicals most likely to be emitted in large quantities are the solvents.

You contact the regional office of the Environmental Protection Agency (EPA) for information on processes used by computer chip manufacturers and the quantities of solvents that might be involved. The environmental specialist searches the Toxic Chemical Release Inventory (TRI) database and informs you that the plant in question is a major emitter of 1,1,1-trichloroethane (TCA); last year, it emitted more than 100,000 pounds of the chemical. The specialist informs you that the plant does not emit significant quantities of the other chemicals on your list. You focus on the cluster of cases and the TCA exposure.

Pretest

(a) What are the major health effects caused by 1,1,1-trichloroethane?

(b) Is 1,1,1-trichloroethane likely to be responsible for the congenital heart defect of your patient's daughter?

(c) What is the Toxic Chemical Release Inventory database that was used by the specialist?

(d) What sources will you use to prepare for the community group meeting? What will you advise?

Answers to the Pretest questions are on page 15.

BEST COPY AVAILABLE

Exposure Pathways

❑ **More than 700 million pounds of TCA are produced in the United States annually.**

1,1,1-Trichloroethane (Cl_3CCH_3) is not known to occur naturally. Originally produced as a safer replacement for carbon tetrachloride and later for trichloroethylene, it has become ubiquitous in the environment. 1,1,1-Trichloroethane is a nonflammable, colorless liquid that evaporates quickly at room temperature. It has a sweet, somewhat sharp odor that can be detected at about 100 parts per million (ppm). (This odor threshold is below the permissible exposure limit [PEL] for the workplace of 350 ppm.)

1,1,1-Trichloroethane is commonly referred to as TCA (used throughout this document). Synonyms for TCA include methyl chloroform, chloroethene, methyltrichloromethane, trichloromethylmethane, alpha-trichloroethane, and alpha-T. TCA should not be confused with TCE, which commonly refers to trichloroethylene ($Cl_2C=CHCl$).

The general population is exposed to TCA through ambient air, contaminated water, or by using household or office products containing the chemical. TCA is found in many building materials, including carpet glues and fabric finishers. The trend toward airtight, highly insulated houses has resulted in higher concentrations indoors than outdoors. In one study, average TCA air levels were about 4 ppb indoors and less than 1 part per billion (ppb) outdoors. Volatilization of TCA from contaminated water during showering, laundering, and other activities can add substantially to indoor exposure.

❑ **For the general population, exposure occurs most often through the many home products containing TCA.**

In a recent EPA study of household products, nearly 250 consumer items contained TCA. Some of these items include the following: fabric water repellants, spot removers, spray shoe polishes, spray paints, paint thinners and removers, pesticides, lubricants for auto door locks, tape and video recorder head cleaners, electric shaver cleaners, and typewriter correction fluids. Some correction fluids and thinners that have high concentrations of TCA are widely abused through inhalation for their narcotic effects. Deaths have resulted from this exposure route despite the mustard oil added to these products to discourage abuse, and some states have banned TCA use in correction fluids and thinners. TCA is also used as a propellant and solvent carrier in some aerosolized bronchodilators. In the past, TCA was used as an anesthetic. In 1990, 705 million pounds of TCA were produced in the United States.

❑ **Airtight, highly insulated homes enhance accumulation of indoor TCA levels.**

TCA is released to the environment by stack and fugitive emissions and in wastewater from the numerous industries that produce or use this compound. It is used in more than 120 industrial classifications (including the defense and electronics industries), primarily as a solvent, vapor degreaser, cold metal cleaner, and propellant. Releases to surface water evaporate quickly, and spills on land dissipate readily through volatilization and leaching. The half-life of TCA in surface water ranges from hours to a few weeks, depending on wind and water turbulence. Bioaccumulation does not occur to a significant degree.

In soil, TCA undergoes slow degradation, and because it is not strongly adsorbed to sandy or clay soils, it can readily leach to underground aquifers. Amounts of TCA in groundwater vary widely by location. In one study of groundwater in 13 U.S. cities, EPA found 23% of the sources contained TCA (maximum concentration 13 micrograms per liter [µg/L] [13 ppb]). Groundwater samples taken near sources of release have been as high as 11,000 ppb.

TCA released to air is transported long distances and will partially return to earth in rain. In the troposphere, TCA degrades very slowly by photooxidation; the half-life is 6 months to 25 years, depending on the intensity of sunlight. Due to the large input of TCA into the atmosphere and its slow degradation, the amount of TCA in ambient air is increasing by 12% to 17% annually. TCA slowly diffuses to the stratosphere where photodegradation is rapid, and the chlorine free radicals that are generated contribute to the destruction of the ozone layer. In 1992, the 93 signatories to the Montreal Protocol, an international agreement to control ozone-depleting substances, agreed to ban TCA and certain other chlorocarbons by 1996, 4 years earlier than previously agreed.

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* Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

Challenge

Additional information for the case study: In a discussion with the environmental engineer at the plant, you learn that within the last 6 months the plant has installed control measures to reduce emissions and is switching to aqueous-based degreasing agents and ultrasonic technology in their cleaning and degreasing processes. He predicts very little will be emitted from the plant in the near future.

(1) What are other possible sources of exposure to TCA for your patient and her neighbors?

Who's at Risk

☐ **Workers involved in operations using TCA are at greatest risk of exposure.**

According to a study conducted by the National Institute for Occupational Safety and Health (NIOSH), more than 1.5 million workers are potentially exposed to TCA. Workers with the greatest potential for exposure to TCA are in the following industries or operations:

auto repair
computer chip manufacture
degreasing and cleaning of metal parts
dry cleaning
electrical parts manufacture
heating and cooling parts during manufacture
mixing and applying commercial resins
photography
solvent recovery
spray painting and gluing
typesetting
waste disposal

☐ **Persons who inhale TCA intentionally for its narcotic properties risk "sudden sniffing death."**

The general population is at risk of exposure through the use of home products that contain TCA, but the levels of exposure associated with normal use have not been shown to cause adverse health effects. Intentional inhalation of TCA for its narcotic effects is a problem, however, and is most common among adolescents. Persons who deliberately sniff glue or solvents to achieve euphoria risk adverse health effects, such as "sudden sniffing death" from cardiac dysrhythmias.

Persons living in homes that use a TCA-contaminated water source risk exposure through ingestion of tapwater, inhalation of volatilized TCA, and dermal contact during showering and laundering. Persons who live near point sources of TCA or near waste disposal sites also risk exposure to above-background levels.

Persons who have histories of alcoholism or severe underlying liver disease may be at increased risk of TCA's adverse effects. Alcohol competitively inhibits the metabolism of TCA. Alcohol and severe liver disease could prolong TCA metabolism and its effects on the central nervous system (CNS).

Challenge

Additional information for the case study: As a result of your work with the community group, you receive a call from a reporter. A wire story indicates that a consumer group had hired a laboratory to test disposable baby diapers and found TCA at 20 ppb in one brand of diapers. The reporter asks whether he should run the story, warning parents that these diapers might have adverse health effects on their babies and challenging grocers to pull the brand from their shelves.

(2) What is your response to the reporter's question?

Biologic Fate

TCA is absorbed efficiently and rapidly through the lungs and gastrointestinal tract and less rapidly through the skin. Steady-state lung retention of 25% to 30% of inhaled TCA in humans is reached within 1 to 3 hours of continuous exposure. Continuous exposure also results in a gradual rise and plateau of arterial and venous blood levels. Increases in pulmonary ventilation or respiratory rate during exercise are not believed to affect changes in the absorbed quantity of TCA after steady-state levels are reached.

☐ **TCA is absorbed efficiently by all routes of exposure.**

TCA is lipophilic and accumulates to a small extent in the body fat. The largest amount of TCA is found in brain tissue, although tissue concentrations throughout the body vary widely. Blood levels correlate highly with levels found in alveolar air. A much greater amount of TCA is absorbed during inhalation exposure than during skin contact.

☐ **Regardless of its route of absorption, most TCA is excreted unchanged through the lungs.**

Regardless of the route of absorption, most TCA (e.g., about 90% of an inhaled dose) is quickly excreted unchanged by the lungs. It has a half-life for elimination from the blood of approximately 53 hours; small amounts of TCA have been detected in the breath several days after exposure has ceased. The remaining 10% of an inhaled dose is excreted unchanged in the urine or metabolized by hepatic cytochrome P-450 mixed-function oxidase enzymes to trichloroethanol and then to trichloroacetic acid. These metabolites can be detected in blood and urine. The half-life of trichloroethanol, which is excreted in urine, is about 9 hours. Because trichloroacetic acid binds to serum albumin, this metabolite persists in the bloodstream with a half-life of about 3 days.

☐ **A small amount of TCA is metabolized in the liver.**

Challenge

Additional information for the case study: Community concern about TCA prompts another patient to call you. He and his wife think their adolescent son is abusing TCA and want you to run some tests to confirm this.

(3) What is your response?

Physiologic Effects

☐ **Primarily the central nervous, cardiovascular, and respiratory systems are affected by acute TCA exposure.**

Fatalities following exposure to anesthetic concentrations of TCA have usually been due to CNS depression, resulting in respiratory arrest. Cardiac dysrhythmias may also occur after exposure to high levels, especially in solvent abusers. Ingestion of TCA may cause immediate burning of the mouth, throat, and esophagus; nausea, vomiting, and diarrhea occur after large ingestions. Because of TCA's defatting action, local skin irritation, erythema, vesiculations, and dermatitis can occur after repeated contact. Stabilizing agents added to TCA, such as epichlorohydrin and dioxane, are sensitizers and may be responsible for some of TCA's dermatologic effects. TCA contact with unprotected eyes can produce transient and superficial tissue effects, including chemosis, hyperemia, and conjunctivitis.

Neurologic Effects

☐ **The principal effect of TCA exposure is CNS depression.**

With increasing concentration of TCA, CNS depression and euphoric narcosis occur in proportion to the amount of TCA absorbed. Mild motor impairment is followed by stupor, coma, and seizures. In acute, high-level exposures, the anesthetic effect occurs rapidly. With chronic exposure, a consistent finding is agitation or lethargy during sedentary periods. Decreased memory and sleep disturbances have also been reported from chronic, low-level exposure.

TCA is lipophilic and accumulates in the central nervous system, resulting in respiratory depression. This depression is mediated, in part, by effects in the brain stem, as well as by generalized CNS narcosis.

Cardiovascular Effects

Acute or chronic exposures to high concentrations of TCA may cause reduced blood pressure and dysrythmias. Sudden death can occur in chronic abusers who inhale TCA. One study suggests that sudden sniffing death from TCA may result from light-plane anesthesia in combination with acute respiratory depression from a medullary chemical lesion. Others suggest that death may be due to a fatal dysrhythmia caused by lowering the myocardial threshold to the effects of epinephrine or other catecholamines.

Tachycardia noted in exposures to low doses and bradycardia observed in exposures to high doses may be controlled by the sympathetic nervous system. If dysrhythmias resolve spontaneously or by treatment, usually no permanent or recurrent problem occurs; however, bouts of premature ventricular contractions, including bigeminy, have been reported to reoccur within 1 to 2 weeks.

☐ **Cardiac dysrhythmias may result from lowering of the myocardial threshold to the dysrhythmogenic effects of epinephrine.**

Respiratory Effects

TCA has a direct irritating effect on the nasal and respiratory mucous membranes. Although this irritant effect is moderate with pure TCA, it can be more severe with technical grade TCA that is stabilized with dioxane or epichlorohydrin. Shortness of breath and chest pain can occur. Acute, high-level exposures to TCA may result in CNS-mediated respiratory depression.

☐ **Respiratory depression associated with TCA exposure is secondary to CNS depression.**

Hepatic and Renal Effects

Hepatic and renal dysfunction can occur 1 to 2 days after a single acute exposure to TCA, as evidenced by abnormal liver function and hepatic lesions. In one study, mild and transient elevation of liver function tests occurred in 33% of workers acutely exposed to high concentrations of TCA. Liver enzymes are often elevated on the first day after exposure, with bilirubin typically rising on the second day. Transient renal damage may also occur as initially evidenced by hematuria and proteinuria. These abnormal test results usually subside within a few days to 1 week, except in persons who have chronic exposures.

☐ **Hepatic and renal dysfunction may occur within 1 to 2 days after TCA exposure.**

Developmental and Reproductive Effects

No data are available on the reproductive or developmental effects of TCA in humans. A multigeneration reproductive study of rats exposed to TCA in drinking water found no reproductive effects. Only one inhalation study found evidence of minor embryotoxicity in experimental animals. No human studies have been reported.

☐ **No data exist to assess the reproductive and developmental effects of TCA in humans.**

Carcinogenic Effects

☐ **No evidence has been reported that suggests TCA is carcinogenic in humans or experimental animals.**

TCA does not appear to be carcinogenic in humans or experimental animals, although the data in humans are limited.

Challenge

Additional information for the case study: The story of your patient and her activities receives national attention. You receive a call from a young woman in another state who has been diagnosed with multiple sclerosis. She had been a secretary for 5 years and used correctional fluids and thinners extensively. She read in the newspaper that these materials contain TCA, as do many household products, and that TCA can cause neurologic effects. She asks you whether TCA could be the cause of her condition.

(4) How will you respond to this question?

Clinical Evaluation

History and Physical Examination

☐ **A thorough work and exposure history is essential to correctly diagnosing TCA toxicity.**

A careful history should first be obtained from the person with suspected exposure, unless life-threatening circumstances exist. Even if serious conditions require immediate treatment, the patient should be questioned while medical care is being given. Family members or friends, as well as emergency medical response personnel, may also be able to provide valuable information regarding exposure.

If the exposure occurred in the workplace, identification of the substance to which the patient was exposed should be verified, if possible, from the container label or a Material Safety Data Sheet (MSDS) or by calling the workplace supervisor. A regional poison control center can help determine ingredients of brand name products and treatment for patients who have been exposed.

Especially in cases of chronic exposure, TCA exposure from all sources must be assessed. These sources include the following: use of TCA-containing household products, nearby industries, a recently remodeled or constructed home, diet, water supply, workplace, hobbies such as furniture refinishing, and recreational activities involving machinery or vehicles. If an airborne exposure is involved, the time the odors were detected and the time of onset of symptoms and their sequence are important. However, the presence of an odor does not necessarily mean that toxic effects will occur because the TCA air level that causes adverse health effects is substantially above the odor threshold. The relative ventilation and amount of TCA vaporized compared to the air volume of the room are important.

After addressing the patient's initial complaints, the physical examination should emphasize the organ systems most likely to be affected by TCA—cardiovascular, pulmonary, central nervous, and gastrointestinal (if ingestion of TCA occurred). Evaluation of the renal and hepatic systems should be assessed through laboratory testing. The patient should be questioned about intercurrent illness and medications, which may compromise the patient's response to toxic exposure.

Signs and Symptoms

Initial symptoms of TCA toxicity include headache, dizziness, fatigue, sleepiness, and nausea. Ataxia, confusion, and stupor can occur with acute exposure. Underlying disorders of the heart and lungs may be exacerbated by TCA exposure. Gastrointestinal signs usually do not proceed beyond nausea in cases of inhalation exposure. Ingestion of TCA may cause vomiting.

☐ **Initial symptoms of overexposure to TCA are neurologic.**

Chronic exposure to levels greater than 350 ppm may result in mild headaches, short-term memory loss, sleep disturbances, and ataxia. The patient should be questioned about other exposures that could be contributory including alcohol and drug abuse, prescription drugs, and psychiatric disorders, as well as exposure to other chemical neurotoxins.

Laboratory Tests

Direct Biologic Indicators

Most of the TCA absorbed by the body is excreted unchanged by the lungs. About 60% to 80% of an absorbed dose is excreted in 1 week, but TCA can be detected in breath weeks after exposure. TCA has an elimination half-life in blood of about 53 hours. TCA blood and breath tests are complex, however, and usually are not available on an emergency basis.

☐ **Generally, only reference laboratories perform tests for TCA blood and breath levels.**

Indirect Biologic Indicators

☐ **TCA metabolites can be measured in blood and urine.**

The metabolites of TCA, trichloroethanol and trichloroacetic acid, can be detected in blood and urine. Trichloroacetic acid binds to serum albumin and will persist in the blood with a half-life of about 3 days. These metabolites can be detected in the urine for a few days after mild exposures and a few weeks after heavy exposures. TCA metabolite measurements are useful if they are markedly elevated compared with normal background levels and if exposure to trichloroethylene, chloroform, and chloral hydrate (which produce the same metabolites) can be excluded.

Mild elevations of liver function tests, such as hepatic transaminases (SGOT or AST, SGPT or ALT), can occur after acute exposures but are usually mild; they most often return to normal after several days. Total bilirubin may also increase. Transient proteinuria and microscopic hematuria are sometimes accompanied by an increase in BUN or serum creatinine.

Challenge

Additional information for the case study: A neighbor of the patient in the case study is an employee at an airline maintenance depot. He has been taking TCA home from work to use as a cleaner for many household chores. His wife, who used it for carpet cleaning, broke out with hives. The condition cleared when her physician prescribed prednisone in tapered doses. The next time she used the TCA, however, the hives returned and became much worse, developing into large confluent splotches. She had had hives several years before when working in a photo lab.

(5) Is TCA the cause of this skin condition? Explain.

Treatment and Management

There are no antidotes for TCA toxicity. Patients should be removed from the contaminated environment as soon as possible, with priority given to ventilatory support, if needed. Supplemental oxygen should be initiated if respiration, pulse, blood pressure, or mental status is compromised. Continuous cardiac monitoring should be maintained until stability is established. Hemodialysis and hemoperfusion have not been proven efficacious.

☐ **Supportive care and removal from the source of exposure are recommended treatment for TCA toxicity.**

Contaminated clothing and personal items should be removed and double-bagged. Skin should be washed with mild soap or detergent and copious water. Care should be taken to avoid secondary contamination of health care personnel from off-gassing vapors or vomitus.

If TCA is splashed in the eye, the eye should be irrigated with water for 15 minutes. If the splash was more than transient, the corneal surface should be stained with fluorescein and examined using a slit lamp. Applying a protective lubricating antibiotic ointment and eye patch usually will enable the cornea to re-form epithelium within 24 to 48 hours.

If TCA is ingested, emesis is not advised because of possible pulmonary aspiration. Gut decontamination with lavage and activated charcoal is recommended if the procedure can be initiated within 2 to 3 hours after ingestion of more than a single swallow of TCA. Protect the airway to prevent pulmonary aspiration. Electrolyte balance should be maintained, and hepatic and renal dysfunction should be monitored until normal.

Chronic exposure to TCA is treated symptomatically. Hepatic and renal function should be assessed. If the exposure was occupational, periodic workplace air monitoring should be carried out to ensure compliance with regulations of the Occupational Safety and Health Administration (OSHA).

Challenge

Additional information for the case study: Testing of private wells in the vicinity of the plant reveals TCA contamination ranging from 30 to 232 µg/L (ppb). (EPA has a standard of 200 ppb in public drinking water supplies.)

(6) Do you expect these residents to manifest symptoms of exposure? What management and treatment would you recommend for the exposed residents?

Standards and Regulations

Workplace

Air

OSHA regulations are based on protecting healthy workers from significant exposure to chemical hazards over a 40-hour workweek. The 1989 permissible exposure limit (PEL) for TCA as an 8-hour time-weighted average (TWA) was set at 350 ppm. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a threshold limit value (TLV) of 350 ppm. ACGIH also recommends a short-term exposure limit (STEL) of 450 ppm. NIOSH recommends that occupational exposures to TCA be controlled so that workers are not exposed to levels greater than 350 ppm (ceiling concentration) as determined by a 15-minute sample (Table 1).

ACGIH has also set guidelines (Biological Exposure Indices [BEI]) for the amount of TCA metabolites in urine of exposed workers. For trichloroethanol, the BEI is 30 milligrams/liter (mg/L) in urine samples obtained at the end of the workweek, and for trichloroacetic acid, the BEI is 10 mg/L.

Table 1. Standards and regulations for 1,1,1-trichloroethane

Agency*	Focus	Level	Comments
ACGIH	**Air-workplace**	350 ppm	Advisory; TLV-TWA†
NIOSH	**Air-workplace**		Advisory; TWA
	Ceiling	350 ppm	
	IDLH §	1000 ppm	
OSHA	**Air-workplace**	350 ppm	Regulation; PEL¶ as TWA
EPA	**Air-environment**	NA**	Under review
	Drinking water	200 ppb	Regulation
	Ambient water	18 ppm	Regulation

*ACGIH = American Conference of Governmental Industrial Hygienists. EPA = Environmental Protection Agency. NIOSH = National Institute for Occupational Safety and Health. OSHA = Occupational Safety and Health Administration

†TLV-TWA (threshold limit value–time-weighted average) = time-weighted average concentration for a normal workday and a 40-hour workweek to which nearly all workers may be repeatedly exposed without adverse effects.

§IDLH (immediately dangerous to life and health) = represents the maximum concentration from which, in the event of respirator failure, one could escape within 30 minutes without a respirator and without experiencing any escape-impairing (e.g., severe eye irritation) or irreversible health effects.

¶PEL (permissible exposure limit) = level in air to which a worker may be exposed, averaged over an 8-hour workday.

**NA = not available

Environment

Water

EPA has set a standard of 200 µg/L (200 ppb) of TCA for drinking water. To protect fish and wildlife, EPA has set the ambient water level at 18 mg/L (18 ppm).

Air

EPA currently has an ambient air standard under review.

ATSDR

Suggested Reading List

General

Astrand I. Uptake of solvents in the blood and tissues of man: a review. Scand J Work Environ Health 1975;1:199-218.

Baselt RC, Cravey RH. Trichloroethane. In: Disposition of Toxic Drugs and Chemicals in Man. Chicago: Year Book Medical Publishers, 1989:824-7.

Caperos JR, Droz PO, Hake CL. 1,1,1-Trichloroethane exposure, biologic monitoring by breath and urine analyses. Int Arch Occup Environ Health 1982; 49:293-304.

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Wallace L, Pellizzari E, Hartwell T. Concentrations of 20 volatile organic compounds in the air and drinking water of 350 residents of New Jersey compared with concentrations in their exhaled breath. J Occup Med 1986;28:603-8.

Specific Health Effects

deNevers N. A fatal fire with "nonflammable" methyl chloroform. Arch Environ Health 1986;41:279-81.

Halevy J, Pitlik S, Rosenfeld J. 1,1,1-Trichloroethane intoxication: a case report with transient liver and renal damage, review of the literature. Clin Toxicol 1980;16:467-72.

Kurt TL, Gallagher JS. Neonatal exposure to methyl chloroform in tape remover. Vet Human Toxicol 1990;32:43-5.

King GS, Smialek JE, Troutman WG. Sudden death in adolescents resulting from inhalation of typewriter correction fluid. JAMA 1985;253:1604-6.

McLeod AA, Margot R, Monaghan MJ. Chronic cardiac toxicity after inhalation of 1,1,1-trichloroethane. Brit Med J 1987;294:727-9.

Perry GF, Jr. Trichloroethane and connective tissue disorders. J Occup Med 1992;35:5-6.

Related Government Publications

Agency for Toxic Substances and Disease Registry. Toxicological Profile for 1,1,1-Trichloroethane (Draft). Atlanta: US Public Health Service, Agency for Toxic Substances and Disease Registry, 1990. Draft report TP-90-27.

Environmental Protection Agency. Household solvent products: a national usage survey. Washington, DC: US Environmental Protection Agency, Office of Toxic Substances, 1987. Report No. EPA-OTS 560/5-87-005.

Environmental Protection Agency. Household solvent products: a "shelf" survey with laboratory analysis. Washington, DC: US Environmental Protection Agency, Office of Toxic Substances, 1987. Report No 560/5-87-006.

Sources of Information

More information on the adverse effects of 1,1,1-trichloroethane and treating cases of exposure to TCA can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: 1,1,1-Trichloroethane Toxicity* is one of a series. To obtain other publications in this series, please use the order form on the inside back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of the Director, at (404) 639-6204.

Answers to Pretest and Challenge Questions

Pretest questions are on page 1. Challenge questions begin on page 3.

Pretest

(a) Chronic, low-level TCA exposure produces primarily neurologic effects including agitation, lethargy, decreased memory, and sleep disturbances. Chronic abuse of TCA may cause cardiac dysrhythmias and central nervous system depression leading to respiratory arrest.

(b) There is no evidence in humans or animals that TCA causes congenital heart defects at any air level.

(c) The Toxic Chemical Release Inventory (TRI) is mandated by the federal government as part of community right-to-know legislation. Industries must report annually the chemicals they discharge to the environment and an estimate of the amounts. This information is incorporated into a database, which is organized by geographic location (state and county) and by chemical. Citizens may access TRI to determine the major sources of environmental release in their vicinity and the chemicals causing that pollution.

(d) Sources that will assist you in preparing for the group meeting are standard toxicology books, on-line databases, and journal articles. In addition, you could talk to persons at ATSDR, the state health department, EPA, the regional poison control center, the trade association for the electronics industry, and health and safety personnel at the plant.

At the meeting, you could discuss your findings, then tell the audience about the effects of TCA, pointing out areas where health data are incomplete or unavailable. You could explain that different levels of exposure to TCA can occur and include deliberate inhalation abuse (air concentrations in thousands of ppm), legal workplace levels (air concentrations to 350 ppm), and environmental levels (typically lower than workplace levels). Because some of the people could smell the solvent outdoors, one may assume the concentration was above 100 ppm, the odor threshold for TCA. However, EPA currently has no ambient air standard for TCA, so it is difficult to assess the risk. You could also explain to the audience that events such as birth defects or cancer could occur in random clusters.

There is no evidence that TCA causes heart defects. However, exposures to any source of TCA should be minimized, and you might discuss how exposures could occur. Your advice might be that the group express their concerns to officials at the plant and that they contact the local or state health department to request investigation of the problem through air and water measurements, air and water modeling, and further epidemiologic investigations.

Challenge

Challenge questions begin on page 3.

(1) TCA is in many household products as a degreaser, solvent, or propellant. Commonly used products are fabric water repellants, spot removers, spray shoe polishes, spray paints, and paint thinners and removers. Household and office exposures can also occur from off-gassing of carpet and fabric drapes if the building is newly built or recently remodeled. TCA is in many aerosolized medications, such as bronchodilators. It is important to have adequate ventilation indoors, especially if any of these products are used in significant amounts or are spilled.

It would not be unusual for the computer chip manufacturing plant to store TCA in underground storage tanks. Leaking storage tanks at electronics plants have been reported to contaminate groundwater in several areas. Testing the community's water supply could help to determine whether leaking underground tanks are contributing to TCA exposure.

(2) You tell the reporter that he should not run the story and falsely alarm parents. You then attempt to put the information in perspective for the media representative. Under EPA rules, drinking water may contain up to 200 µg/L (200 ppb); bathing water may contain up to 18,000 ppb. You are not aware of a TCA standard for disposable diapers. While it is true that children are more susceptible to many toxicants and often exhibit signs of poisoning at lower levels than adults (e.g., lead or organophosphate pesticide exposures), the TCA level of 20 ppb is not cause for alarm. You further explain that TCA is one of the less hazardous solvents in terms of health effects. The level of TCA found is also not likely to cause diaper rashes, which occur in more than 20% of infants in the first 6 months of life.

(3) The best test for confirmation of exposure is the measurement of TCA in the blood. If TCA is detected in the blood, the adolescent most likely inhaled it within the last 5 to 7 days. If TCA metabolites (trichloroethanol or trichloroacetic acid) are also detected in the same blood sample, he may be a chronic abuser. TCA is quickly exhaled from the lungs; therefore, TCA metabolites are not likely to be present after a one-time use.

An approach that requires biologic testing is a bit adversarial, however. Rather, both parents should educate their son about the hazards of inhalant abuse. They should get involved in closely monitoring their child's activities. If school performance is deteriorating or they have other reasons to suspect their son's activities, enrolling him in a community substance abuse program and enlisting the help of a mental health professional to explore why their son is taking such risks may be appropriate. Inhalation abuse of solvents is most common in adolescents, and many states have mandated restrictions on selling spray paints and solvents to juveniles.

(4) TCA exposure has not been associated with multiple sclerosis (MS). MS is the most common chronic disease of the central nervous system in young adults in North America. It is characterized by the occurrence of discrete areas of demyelination or plaques in the brain or spinal cord with symptoms including some degree of paralysis, nystagmus, and disturbances of speech, depending on the site of the lesions.

(5) Although degreasing or defatting skin of endogenous oils is the most common skin problem with TCA, contact dermatitis, hives, and urticaria have been reported, usually associated with a history of these conditions. These allergic conditions are associated with use of TCA in a stabilized form, which contains dioxane or epichlorohydrin. Both of these stabilizers are not only stronger irritants than TCA, but also skin sensitizers. (See *Case Studies in Environmental Medicine: Skin Lesions and Environmental Exposures.*)

(6) The appearance of symptoms will depend upon dose, duration, and route of exposure. The routes of exposure include ingestion of the contaminated water and inhalation and dermal exposure during showering, laundering, or cleaning. The highest level found is not significantly above the EPA regulation. The mean daily intake of TCA from all sources (air, food, and water) has been determined to be between 50 and 1000 µg/day; therefore, one would not expect symptoms in most people. Because children and elderly persons are generally more susceptible to toxic agents, households with these occupants could consider changing their source of water.

OBSERVATION

Trimethyltin Encephalopathy

Robert G. Feldman, MD; Roberta F. White, PhD; Ikechukwu I. Eriator, MD

A chemistry student was acutely exposed to vapors of an organotin compound. Seventy-two hours later, he exhibited delirium, spatial disorientation, perseveration, inappropriate affect, and memory defects. Five months later, he experienced episodes of complex partial seizures, which continue to require anticonvulsant medication after 7 years. Trimethyltin was identified in blood and urine samples taken 17 days after the accident; the blood level of trimethyltin was elevated 35 days after exposure. Serial electroencephalograms showed persistent left temporal paroxysmal epileptogenic potentials. Serial neuropsychological tests revealed persistent memory defects, cognitive dysfunction, and dysphoria 4 years after exposure. We review acute, resolving, and long-term residual neurotoxic effects of trimethyltin in man. We describe detailed clinical observations, serial neuropsychological test results, electroencephalographic findings, and exposure data in this patient, confirming the limbic system effects of trimethyltin and relating them to the known histopathologic pattern of this condition.

(Arch Neurol. 1993;50:1320-1324)

Toxicologic reports indicate involvement of the central nervous system by alkyltins. Triethyltin intoxication has been used as an experimental model of myelinopathies, neurodegenerative disorders, and cerebral edema, while trimethyltin has been used in the investigation of hippocampal lesions, kainic acid neurotoxicity, and minimal brain dysfunction and to elucidate the cytoarchitecture of the brain and the neuropathologic findings of limbic seizure activity.[1,2]

Although there are many reports from studies on laboratory animals on the neuropathologic and behavioral changes induced by trimethyltin,[3] there have been few reports on such effects in humans[4-7] and those that do exist are confounded by exposure to chemicals other than tin, poor exposure data, or incomplete clinical follow up (**Table 1**).

We describe the acute, resolving, and long-term effects of trimethyltin in a 23-year-old man exposed to this alkyltin through dermal and inhalational routes.

REPORT OF A CASE

A 23-year-old male graduate student, without a significant medical history, was trying to recrystallize an alkyltin compound, *bis*-trimethyl-stannyl-acetylene, from an ether-based solvent when it accidentally ignited. An explosion and fire resulted in burns (12% first-degree, 2% second-degree, and less than 1% third-degree burns) mainly on the left side of his head, neck, and chest. Although stunned, he had no loss of consciousness. Apart from a renal tubular acidosis (bicarbonate, 17 mmol/L) that resolved after vigorous fluid and electrolyte therapy, other features were essentially neurologic and neurobehavioral.

On admission to the hospital, he was oriented and demonstrated no obvious neurologic deficits. Three days later, he appeared to be confused and disoriented; he

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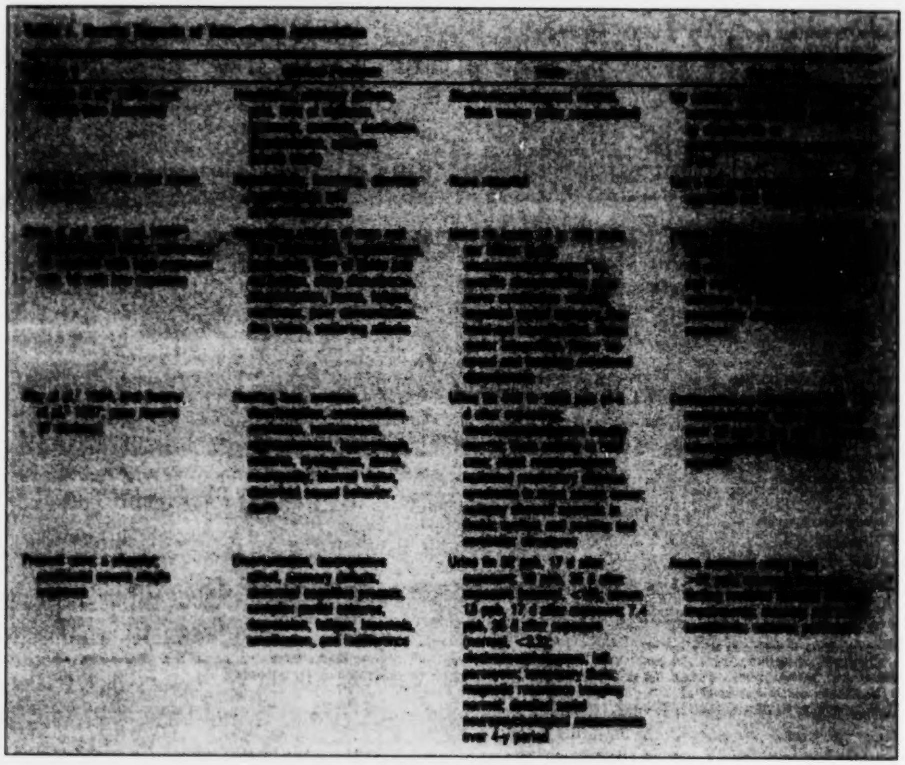


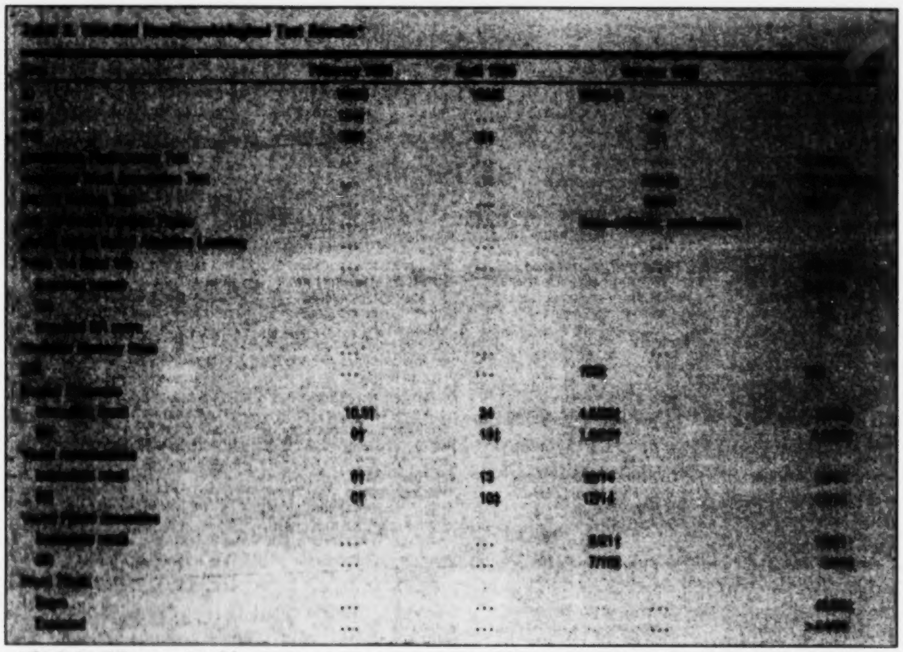
could not find the bathroom or remember his visitors. He was disoriented to place and time. He mumbled repetitive statements to himself about the accident. Gait was normal. Tendon reflexes were 2+ equally. He was without pathologic reflexes, and the results of his sensory examination were normal. There was no papilledema. A computed axial tomographic scan was normal. An initial electroencephalogram showed 4- to 5-Hz paroxysmal theta waves over the left temporal area. Asymmetric 3- to 4-Hz delta waves developed on the left side with drowsiness or hyperventilation. Neuropsychological testing revealed significant impairment in new learning of verbal and visuospatial information on the Wechsler Memory Scale–Revised (WMS-R) and performance on the visual-motor and visuospatial subtests of the Wechsler Adult Intelligence Scale–Revised (WAIS-R) were only average. A performance IQ (PIQ) equal to 106 was well below the PIQ of 124 earned in a school assessment 2 years prior to the accident.

Repeated (partial) neuropsychological testing done 10 days after exposure showed some recovery of cognitive function. A PIQ was then identical to premorbid levels. Immediate recall of verbal and visuospatial information on the WMS-R improved, but his delayed recall continued to show forgetfulness (46% on the verbal task and 23% on the visuospatial task).

Urine and serum tin assays done on the 17th day after exposure showed 13 parts per billion (ppb) of trimethyltin (normal, <3.3 ppb). The trimethyltin concentration was still elevated (7.4 ppb) on the 35th day after exposure. The initial urinary trimethyltin level was 52 ppb (normal, <18 ppb), but this had fallen to 10 ppb by the 35th day after exposure (analyses by gas chromatographic mass spectrography, National Medical Services, Willow Grove, Pa).

His memory had not stabilized by the time he was discharged 18 days after exposure. He became lost in his hometown and his parents complained that he was "acting strange" and could not recall information presented to him.

A repeated electroencephalogram 3 months after exposure continued to show excessive scattered slow fre-



*IQ indicates intelligence quotient; PIQ, performance IQ; VIQ, very superior IQ; WAIS, Wechsler Adult Intelligence Scale; WAIS-R, WAIS-Revised; DR, delayed recall; and MQ, memory quotient. See White et al[30] and White and Proctor[31] for a description of the test battery.

†Moderately severely impaired for IQ.

‡Mildly impaired for IQ.

quencies bilaterally, with persistent theta instability over the left hemisphere. When he tried to return to school 4 months after exposure, he could not recall details of his thesis and was unable to continue his work. Five months after exposure, he experienced interrupted awareness on two occasions. His friends described the second episode thus: "his eyes bulged out, he began to shake all over, and he nearly fell out of the chair."

When seen at 19 months after exposure, he complained of recurrent blackouts of both mild and severe types; the latter was preceded by an aura of visual disturbance, sense of an unpleasant smell, feeling of familiarity, and intense sweating. He also complained of difficulties with sleep, concentration, and recall. Neurologic examination revealed no motor or sensory deficits. Brainstem auditory evoked response, somatosensory evoked potentials, and visual evoked potentials continued to be normal as they had been on discharge. Repeated EEGs continued to show intermittent paroxysmal theta slowing in the left temporal area.

Neuropsychological assessment (including WAIS-R, Ravens Advanced Progressive Matrices, Repeated Motor Programs, Trail Making Test, Wisconsin Card Sorting Test, Hand Grip Strength, Finger Tapping, Grooved Pegboard, Boston Naming Test, Controlled Word List Generation, Writing Sample, Boston Visuospatial Quantitative Battery Constructions, Rey-Osterreith Complex Figure, WMS [Revised], California Verbal Learning Test, Milner Faces, Albert's Famous Faces, Minnesota Multiphasic Personality Inventory, and Profile of Mood States) at this time revealed very superior IQ scores (**Table 2**). He performed below expectation on a coding task (WAIS-R Digit Symbol), but most of the other attention, language, and spatial tasks were performed at superior levels. However, memory quotient on the Wechsler Memory Scale (WMS) remained below expectation at 106. Learning of narrative information was well below expectation, with forgetting on delay. Multiple-choice testing of recognition memory was also impaired on this task. He was also impaired in IQ for learning WMS verbal paired associates and lost 2/9 (22%) on delayed recall; learning and recall were well below expectation for IQ on the California Verbal Learning Test (12/16 on Trial 5). Memory for visual designs was within expected limits on immediate and delayed recall. Depression and helplessness were noted on behavioral/personality inventories.

NEUROPSYCHOLOGICAL ASSESSMENT 43 months after exposure (Table 2) revealed an improved score on the omnibus memory test (WMS Memory Quotient=120). However, he continued to evidence mild memory deficits. Forgetting of verbal (but not visuospatial) information was seen on WMS verbal memory tests, California Verbal Learning Test, and difficult paired associate learning. Performance on a memory test requiring the patient to learn new information despite interference from a distraction task (Peterson-Peterson Word Triads task) was below expectation for his IQ. He also reported symptoms consistent with depressive affect on the Minnesota Multiphasic Personality Inventory. Overall, neuropsychological test findings were considered to be consistent with dysfunction localized to the limbic system, particularly the left mesial temporal (hippocampal) area.

Magnetic resonance imaging of the brain at this time was normal. The electroencephalogram continued to show left temporal theta activity with rare sharp wave and rhythmic discharges.

COMMENT

Trialkyl forms of tin have been associated with severe acute neuropsychologic manifestations in clinical and environmental settings. Of 270 known cases of poisoning following the contamination of an antibiotic by triethyltin, only 10 were said to have recovered completely. Over 100 victims died, while many were left permanently disabled.[8] An acute limbic-cerebellar syndrome was reported in six industrial workers who cleaned a tank containing trimethyltin. One died, while two were left permanently disabled.[7,9] Two chemists were exposed in a poorly ventilated laboratory and they developed seizures as well as memory and confusional disorders.[4] In another report,[6] when 22 workers were exposed in a poorly ventilated situation, the four individuals followed up had long-term changes in personality, probably due to irreversible central nervous system changes.

The trimethyltin syndrome has been produced in rats and consists of tremor, hyperactivity, aggression, self-mutilation, and spontaneous seizures. This constellation of behavioral changes probably is attributable to limbic system pathology.[10] Higher doses may be associated with perseverations. A consistent observation has been impaired retention in inhibitory avoidance paradigms and long-lasting impairments in acquisition and retention of both food- and shock-motivated responses.[1]

Histopathologic studies in laboratory animals have shown a preferential vulnerability of the hippocampus. Early pathologic changes have been noted in the pyramidal cells of areas CA2 and CA3 of the hippocampus as well as in the granule cells of the dentate gyrus.[5,11,12] Damage also occurs in the amygdala, neocortex, pyriform cortex, entorhinal cortex, and olfactory bulbs. Damaged areas in the forebrain are those associated with learning and memory impairment in animals or dementia and amnestic syndromes in humans.

Our patient manifested overt abnormal neurobehavior 3 days after the accident. This "latent period" has been noted in animal studies[10,12,13] as well as in previous human exposure.[7,9] A peak brain tin concentration on about the fourth day has been observed in animal experiments,[13] though total brain tin levels in such animals may not necessarily correlate with the degree of central nervous system toxicity.[14] It is likely that trimethyltin was responsible for this encephalopathy in view of the fact that other organotin compounds undergo biotransformation by dealkylation.[15] Trimethyltin is a stable metabolite,[16] and trimethyltin was the only form of organotin found in the patient's blood and urine assays.

Increased urinary levels of trimethyltin are consistent with significant body content of trimethyltin. Review of data from a previous report[9] indicates that the maximum urinary levels occur 4 to 10 days after exposure. This patient may, therefore, have had a significantly higher content in the first few days after exposure than that measured in the first urine sample taken 17 days after exposure. The serum level was still elevated 35 days after exposure. This may have been due to high body content and, possibly, to binding of trimethyltin to erythrocytes,[2] though the latter has not been clearly documented in primates or man.[17] In fact, the lower trimethyltin-hemoglobin binding capacity in mice and humans compared with rats may explain the increased sensitivity of mice and humans to the effects of trimethyltin.[18]

This case is similar to the other reported human cases in manifesting with memory defects, confusion, incongruous affect, disorientation, seizures, depression, insomnia, poor vigilance, and slow and paroxysmal electroencephalographic records in keeping with a toxic encephalopathy. Perseverations, though observed in animal studies,[19] have not been previously documented in humans and were seen rarely in this patient. Hyperactivity, aggression, or alternating attacks of rage and deep depression reported in other human subjects were also not present in this patient.[20-22]

Classic evidence of focal cerebral dysfunction, with impairments in new learning such as those seen in mesial temporal lobe damage, is present in this patient.[23] Interestingly, the memory findings were in the verbal realm and, therefore, suggestive of lateralized left temporal dysfunction. Likewise, his dysphoric mood is typical of mood changes associated with left hemisphere damage.[24-27] The lateralization of mood and memory changes to the left cerebral hemisphere is consistent with both the patient's EEG findings and findings previously reported in patients with left temporal foci excision and seizures not attributable to toxic exposures.[28]

The only available human autopsy report described a man who died of pulmonary effects secondary to high exposure.[7,9] Morphologic alterations in the brain were most prominent in the amygdala, temporal cortex, basal ganglia, and pontine nuclei. Swollen perikarya, loss of Nissl substance, and necrosis of nerve cells were seen. Electron microscopy showed zebra bodies and many vacuoles. Cerebral edema with irreversible cell damage also occurred in the amygdala. The cerebellar cortex showed loss of Purkinje cells.

The exact mechanism of neurotoxic action of trimethyltin remains uncertain. Proposed mechanisms include release of endogenous excitotoxins from the heavy metal–containing pathways of the hippocampus,[29] elevated extracellular glutamate levels,[30] hyperammonemia,[31] decreased γ-aminobutyric acid concentration,[32] inhibition of Ca_{2+}-ATPase in a concentration-dependent manner thereby interfering with calcium pump and other cAMP (adenosine 3′,5′-cyclic phosphate)-mediated processes in the brain,[33] or a reduction in the hippocampal zinc concentration, possibly leading to mossy fiber disinhibition and subsequent hyperexcitation of the hippocampal electrical circuitry.[3,34]

Trimethyltin is an intermediate by-product in the production of other more commonly used tin products.[3] It, thus, still constitutes an occupational hazard for some groups, especially chemists who often seem unaware of the inherent dangers.[35] This article documents the acute and long-term neurotoxic effects of exposure in a young man. The detailed serial electroencephalographic and neuropsychological studies provide a basis for estimating the prognosis in such cases.[1]

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ATSDR January 1992

Case Studies in Environmental Medicine

6 . Trichloroethylene Toxicity

Environmental ALERT...

☑ *Trichloroethylene (TCE) is a common industrial solvent and contaminant of hazardous waste sites, groundwater, and drinking water.*

☑ *TCE is a CNS depressant and a suspected hepatotoxin in humans.*

☑ *EPA considers TCE an animal carcinogen and a potential cancer hazard to humans.*

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. The Agency for Toxic Substances and Disease Registry (ATSDR) and the Centers for Disease Control (CDC) designate this continuing medical education activity for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association and 0.1 continuing education units for other health professionals. See pages 21 to 23 for further information.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

Concerns of a young family exposed to TCE-contaminated drinking water

Your practice is in a suburban community with a number of high-technology industries. A couple for whom you have been the family physician asks for an appointment to discuss their daughter's illnesses and a matter of concern to them.

During the initial consultation, the mother reports that they are living in an area supplied by municipal well water. They have recently received a notice from the municipal water district stating that their drinking water contains 100 parts per billion (ppb) trichloroethylene (TCE), and as a precaution, they are being supplied with bottled drinking water until an alternative well can be put into service. The notice indicates that the well water is suitable for bathing and laundering. The father interjects that he is familiar with TCE; it is used in the electronics plant where he works.

The daughter, aged 4, has had a number of ear infections during her first 2 years, culminating in a myringotomy at age 3. Follow-up by an ENT specialist has shown normal hearing. Although there have been no further infections, the mother stresses that her daughter seems to have a greater number of colds than her classmates and "has not seemed as healthy as she should be." However, the daughter's chart does not reflect an unusual number of office visits or calls. The mother also notes that the child's day-care center is next to "some kind of machine shop" where a chemical odor has been noticed recently. Several of the children and one of the teachers have complained of eye and throat irritation in association with the odor.

The mother, who is 33 years old, then reveals that she may be pregnant and she has had mild nausea for 1 week. It has been 8 weeks since her last menstrual period. Both parents are concerned about the possibility that the TCE in the drinking water might have affected the fetus. Although this pregnancy was planned, they might consider terminating the pregnancy if the baby was likely to be "damaged." They are also concerned that the entire family might suffer from cancer or other diseases in the future.

Before receiving bottled water, the family drank tap water when thirsty and made coffee with tap water. Tap water also was used for cooking and brushing their teeth, and is still used for bathing. They have never noticed discoloration or an off-taste to the tap water. They encourage their child to drink water instead of sodas during the summer and estimate the amount of water each of them consumes is 2 to 3 glasses a day.

You schedule each parent and the child for an individual office visit.

Pretest

(a) What would you include in the mother's and daughter's problem list?

(b) What additional information would you seek before seeing the family again?

(c) What reassurances might you provide at the end of this initial visit?

Answers to the Pretest can be found on page 19.

Exposure Pathways

- **The odor threshold of TCE is 20 to 80 ppm, which may not provide adequate warning of toxic levels.**
- **The most common sources of nonoccupational exposure to TCE are ambient air and drinking water.**

Trichloroethylene or TCE ($Cl_2C=CHCl$) is a clear, colorless, nonflammable liquid possessing a sweet, fruity odor characteristic of chloroform. The odor threshold is approximately 20 to 80 parts per million (ppm). For some workers, TCE's odor may not be detectable at concentrations near the permissible workplace exposure limit of 50 ppm (as determined by an 8-hour time-weighted average), and so may not provide adequate warning of its presence.

The official chemical name of trichloroethylene is trichloroethene. Other synonyms include TCE, TRI, acetylene trichloride, and ethylene trichloride. Trade names for this industrial solvent include Benzinol, Circosolve, Flock Flip, Narcogen, Perm-A-Chlor, Tri-clene, and Vestrol.*

TCE does not occur naturally; therefore, its presence indicates manufacture, use, or storage. Eighty percent of TCE is used for vapor degreasing of fabricated metal parts in the automotive and metal industries. Consumer products that contain TCE include typewriter correction fluids, paint removers/strippers, cosmetics, adhesives, spot removers, and cleaning fluids for rugs. Prior to its ban for certain applications in 1977, TCE was also used as a general (mostly obstetrical) anesthetic, analgesic, grain fumigant, disinfectant, pet food additive, and extractant of spices in foods and caffeine in coffee.

Occupational exposures may occur in chemical industries that manufacture polyvinyl chloride, pentachloroethane, and other polychlorinated aliphatic hydrocarbons, flame retardant chemicals, and insecticides. Other potential exposures occur in manufacturing processes of disinfectants, pharmaceuticals, dyes, perfumes, and soaps. Mechanics, oil processors, printers, resin workers, rubber cementers, shoe makers, textile and fabric cleaners, tobacco denicotinizers, varnish workers, and dry cleaners also have increased likelihood of TCE exposure, although most dry cleaners now use tetrachloroethylene (perchloroethylene) or 1,1,1-trichloroethane.

In the workplace, TCE is seldom present as a pure substance. Industrial grade TCE contains small amounts of stabilizers in the form of antioxidants or acid receptors; total chemical impurities usually do not exceed 0.1% by weight. Decomposition of TCE into dichloroacetylene (a neurotoxic compound) and phosgene

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* Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services

(a serious pulmonary irritant) occurs in the presence of alkali at temperatures above 60°C for the unstabilized compound and above 130°C for the stabilized compound.

Because of its widespread use, TCE has become a common environmental contaminant. Contamination results from evaporative losses during use; discharge to surface waters and groundwater by industry, commerce, and individual consumers; leaching from hazardous waste landfills into groundwater; and from the incidental addition of TCE during food production.

In the atmosphere, TCE is destroyed by photooxidation, with a half-life of less than 7 days. This relatively short half-life significantly limits the transport of TCE in air; however, the continual volatilization of TCE from emission sources or contaminated surface waters ensures its persistence in air. Examination of arctic air between 1982 and 1983 demonstrated mean TCE levels of 8 to 9 parts per trillion (ppt). This compares to mean concentrations of 30 ppt TCE in rural or remote areas, 460 ppt in urban and suburban areas, and up to 1200 ppt in areas nearest emission sources. Surveys have detected TCE in at least 460 of 1177 hazardous waste sites on the U.S. Environmental Protection Agency's (EPA) National Priorities List, with a maximum level of 12,300 ppt TCE in the ambient air at one New Jersey site.

TCE in drinking water is a result of its rapid leaching from landfills and its discharge from industrial wastewaters. TCE volatilizes quickly from water depending on temperature, water movement, and aeration. The biodegradation of TCE under anaerobic conditions is slow, making TCE relatively persistent in subsurface waters. An EPA groundwater survey detected TCE in approximately 10% of the wells tested. TCE is estimated to be in 34% of the nation's drinking water supplies.

Because of TCE's volatility, household activities such as bathing, laundering, and cooking with contaminated water may produce TCE air concentrations above normal ambient levels. Both natural and processed foods may contain TCE because of direct uptake through the environment, contamination of water used in food processing, and contamination by solvents used in cleaning food processing equipment. Most processed foods examined contain levels of a few parts per billion. Studies indicate that TCE does not bioaccumulate in the food chain.

Challenge

(1) What are the possible sources of exposure to trichloroethylene for the family described in the case study?

Who's at Risk

- ☐ **Workers in metal fabricating and cleaning operations have the greatest likelihood of exposure to high concentrations of TCE.**
- ☐ **Because TCE inhalation can cause euphoria, deliberate abuse may occur.**
- ☐ **Ingestion of alcohol may potentiate the CNS depressant effects of TCE.**
- ☐ **A small subset of the population may be predisposed to developing ventricular fibrillation or asystole after exposure to high concentrations of TCE.**

Most significant exposures to TCE occur in the workplace. The National Institute for Occupational Safety and Health (NIOSH) has estimated that 3.5 million workers in the United States are exposed to TCE, with the majority of high exposures ascribed to metal degreasing operations. Sudden death has occurred in apparently healthy workers exposed to concentrations exceeding current legal workplace standards and in solvent abusers deliberately sniffing typewriter correction fluid from plastic bags or in enclosed spaces. Some of these deaths were due to asphyxia, whereas others were attributed to either ventricular fibrillation or asystole. Although no human studies have directly assessed potential dysrhythmogenic effects of TCE, there is no evidence that persons exposed to TCE at background environmental concentrations or at allowable workplace levels are at increased risk of developing cardiac dysrhythmias.

Until 1977, when certain uses were banned, TCE was employed as an inexpensive, nonflammable, and self-administered obstetrical anesthetic (Tri-lene*). It was discovered that alkali in rebreathing systems could lead to the production of dichloroacetylene, which produced cranial nerve injuries. Workers in environments containing this TCE-decomposition product also could be at risk of developing trigeminal, optic, or facial nerve effects.

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* Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

Alcohol potentiates TCE's effects on the central nervous system. Concurrent alcohol consumption and exposure to TCE can result in "degreaser's flush," a temporary redness and itching of the back, neck, and face. Theoretically, liver dysfunction or disulfiram (Antabuse®[*]) treatment could reduce the metabolism of TCE and thus increase its CNS depressant effects.

TCE is one of the volatile organic contaminants most frequently found in groundwater. The possibility of an association between ingested TCE and long-term effects, including malignancies, has been raised, but scientific evidence proving that these effects are due to TCE exposure is lacking. To gather information on the health effects of ingesting TCE-contaminated water, ATSDR, in cooperation with the States, has established a national registry. This registry is discussed in Sources of Information, page 20.

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[*] Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

Challenge

(2) Which members of the family described in the case study are at increased risk for ***adverse*** *effects from TCE? Explain.*

Biologic Fate

- **Pulmonary and gastrointestinal absorption of TCE is rapid; dermal absorption is relatively slow.**
- **TCE metabolism occurs mainly in the liver.**
- **Species differences in TCE metabolism require that caution be used in extrapolating adverse effects to humans.**

At 100 to 200 ppm TCE, the lungs of human volunteers absorbed approximately 50% of an inhaled dose during the first 30 minutes of exposure. Case reports of human poisoning after ingestion of TCE indicate that gastrointestinal absorption is also substantial. Dermal TCE absorption in humans may add to the body burden, but toxicity from this source alone is unlikely. In contrast to direct contact of the skin with liquid TCE, absorption of its vapor through the skin is negligible.

Once absorbed, TCE is rapidly cleared from the blood. Due to its lipid solubility, TCE accumulation occurs in organs containing high levels of adipose tissue. Data from animal studies indicate that body fat, adrenal glands, ovaries, and cellular components of the blood accumulate the greatest portion of absorbed TCE. TCE rapidly crosses the placenta in both humans and animals, and can accumulate in the fetus.

In humans, TCE is metabolized primarily in the liver by the mixed function oxidase system that probably converts TCE to an oxide (epoxide). Subsequently, this reactive intermediate may rearrange to trichloroacetaldehyde and then chloral hydrate, the latter forming the trichloroethanol and trichloroacetic acid metabolites excreted in the urine after TCE exposure. At 54 to 140 ppm TCE, human volunteers metabolized approximately 90% of an inhaled dose. No studies have provided evidence of saturation of TCE metabolism in humans, at least for inhaled concentrations to 300 ppm.

A relatively small amount of absorbed TCE is exhaled unchanged; most of an absorbed dose is metabolized and excreted in the urine. After exposure to air concentrations between 100 and 200 ppm, approximately 30% to 50% of an absorbed dose appears in urine as trichloroethanol, and about 10% to 30% appears as trichloroacetic acid. The time between TCE inhalation and urinary excretion of trichloroethanol is relatively short (biologic half-life approximately 10 hours) compared with the urinary excretion of trichloroacetic acid (biologic half-life approximately 52 hours). Trichloroacetic acid is theoretically detectable in urine for at least a week after TCE exposure.

Challenge

(3) Additional information for the case study: On the next visit to your office, the mother states that some families in their neighborhood are being seen by another practitioner, who has sent specimens to a laboratory for measurement of indicators of trichloroethylene exposure.

What biologic indicators of TCE exposure are likely being measured?

(4) If biologic measurements are performed, what considerations should be taken into account to properly interpret the results?

Physiologic Effects

Studies in humans show that TCE produces CNS effects, mucous membrane, skin, and gastrointestinal irritation, decreased appetite, and headache. However, these results are inconsistent with those of better designed studies. Hepatotoxicity has been associated primarily with intentional TCE inhalation abuse. Renal failure has been reported in concert with confirmed hepatic damage. Cardiac dysrhythmias due to TCE exposure may be induced in susceptible persons.

Central Nervous System Effects

TCE-induced CNS symptoms depend on both concentration and exposure duration. In one study of human volunteers, exposure to TCE air levels of 27 ppm for 4 hours caused drowsiness and mucous membrane irritation, and at 81 ppm, headaches. In another study, drowsiness, lethargy, and nausea were noted within 5 minutes at anesthetic concentrations of 2000 ppm. TCE presumably causes anesthesia by affecting cell membranes and

☐ **CNS depression is the most prominent effect of acute TCE exposure.**

altering neuronal transmission. Symptoms due to short-term exposures typically resolve within a few hours of exposure.

- **Chronic occupational TCE exposure has been associated with neurologic abnormalities.**

In a study of 50 workers employed from 1 month to 15 years in various industrial cleaning and degreasing operations using TCE, complaints due to cnronic exposure included decreased appetite, sleep disturbances, ataxia, vertigo, headache, short-term memory loss, and fewer word associations. Greater frequency of symptoms were noted in workers exposed to higher (85 ppm) than lower (14 ppm) mean TCE concentrations.

In the brains of animals chronically exposed to high concentrations of TCE (1000 ppm to 3000 ppm), histologic changes have been demonstrated, but these changes do not correlate with behavioral abnormalities detected in animals or humans. Persons who have deliberately abused volatile chlorocarbon solvents have developed cerebellar damage and ataxia. Electrophysiologic studies in humans have not detected significant abnormalities of peripheral nerve conduction.

Cardiovascular Effects

- **Death due to cardiac dysrythmia in TCE-exposed workers has been associated with high doses in conjunction with vigorous physical activity.**

Mortality studies of TCE-exposed workers do not indicate an increased risk of cardiovascular death. A few susceptible persons who are exposed to near-anesthetic levels during vigorous activity may have increased risk of cardiac dysrythmia. However, there is no evidence that exposure at high TCE levels causes a predisposition to cardiac toxicity at lower levels. When TCE was administered as an anesthetic agent, serious ventricular dysrhythmias and cardiac arrests were rare and were nearly always associated with hypoxia. Significant ventricular ectopy would not be expected from TCE exposure at background environmental levels or those currently allowed in the workplace.

Gastrointestinal and Renal Effects

- **Case reports associate liver damage with inhalation of high doses of TCE.**
- **Human nephrotoxicity due to TCE exposure is rare and generally occurs in persons with TCE-induced hepatic damage.**

When swallowed, TCE causes gastrointestinal irritation, with possible inflammation of the GI tract manifested as nausea, vomiting, diarrhea, and abdominal pain. Hepatotoxicity has been associated primarily with intentional TCE inhalation abuse. In these cases, hepatic histologic examination has revealed centrilobular necrosis with fatty infiltration. Chronic TCE exposures at concentrations currently permissible in the workplace or at those expected in ambient air are not likely to cause liver damage.

TCE-induced renal failure in humans has been reported, albeit infrequently, and usually in concert with confirmed hepatic damage. One case involved a long-time metal degreaser who developed acute tubular necrosis (confirmed by biopsy), which led to renal failure. Another case involved a worker exposed to 99.5% TCE for 8 hours; he developed allergic interstitial nephritis with secondary tubular necrosis. Animals demonstrate little nephrotoxicity after single, high-dose exposures.

Reproductive and Developmental Effects

No increased incidence of congenital malformations has been detected in babies born to mothers occupationally exposed to TCE. A small cross-sectional study of degreasing workers showed no effect of TCE exposure on male germ cells. Data from animal studies reveal no adverse effects on reproductive system histology, fertility, or other reproductive performance parameters.

☐ **Limited studies in workers have not detected significant reproductive or developmental abnormalities due to TCE exposure.**

TCE crosses the placenta in animals and has been found in human newborns after maternal TCE anesthesia during childbirth. Human developmental effects were attributed to the ingestion of TCE-contaminated water in one study, but the significance of this finding is questionable because of mixed chemical exposures and methodologic inadequacies of the study. In animals, abnormalities (decreased fetal body weight and ossification anomalies) have been reported infrequently.

Carcinogenic Effects

Inhalation or oral exposure to high doses of TCE produces liver and lung tumors in mice, and renal adenocarcinomas, testicular tumors, and possibly leukemia in rats. The relevance of the liver tumor data obtained from the mice used in these studies is controversial because the species used tends to form spontaneous liver tumors. The presence of TCE stabilizers, such as epichlorohydrin, may also confound some of these results. These studies indicate that mice are more susceptible than rats to TCE carcinogenicity.

☐ **The few epidemiologic studies of TCE-exposed persons to determine cancer risk are inconclusive.**

Most early epidemiologic studies of workplace exposures to TCE did not demonstrate a significant increase in the incidence of cancer. A recent follow-up study of workers, however, found excesses of bladder cancer and lymphomas. The significance of this study has yet to be confirmed. Some inconsistencies between results of animal and human studies may be due to metabolic saturation and formation of reactive intermediates that occur in animals exposed to high TCE levels but not in humans after low-level exposure.

EPA considers the weight of evidence sufficient to conclude that TCE is carcinogenic in animals and a probable human carcinogen. However, the animal studies do not meet the National Toxicology Program (NTP) guidelines (i.e., positive carcinogenicity in multiple species of both sexes); therefore, TCE is not listed as a carcinogen in NTP's most recent report.

Other Effects

- ☐ **TCE is a mild respiratory tract irritant and may produce contact dermatitis.**
- ☐ **Evidence does not show that TCE adversely affects the human immune system.**

TCE produces minimal irritation of the respiratory tract except at concentrations exceeding current workplace standards. Use of TCE in anesthetic concentrations did not damage the pulmonary system. TCE is not a sensitizing agent, and bronchospasm is unlikely to occur except in highly susceptible persons after exposure to high concentrations. Rarely are patch tests positive for allergic reaction.

Like other organic solvents, TCE may produce contact dermatitis, rashes, and burns. The defatting dermatitis resulting from prolonged contact may reduce resistance to skin infections. An irritant reaction resembling an exfoliative dermatitis or scarlatiniform reaction may occur from dermal contact with contaminated clothing.

A syndrome called degreaser's flush has been associated with the interaction of ingested ethanol and inhaled TCE. Typically, erythema resulting from vasodilation develops around the face, back, and shoulders within 30 minutes and resolves within an hour of appearance.

No deleterious effects on the immune system have been noted in persons exposed to TCE through environmental sources. Immunologic studies in animals are inconclusive.

Challenge

(5) Additional information for the case study: The father says that he has felt increasingly tired and easily fatigued for the past few months. Results of his physical examination are entirely within normal limits. What tests, if any, would you order?

(6) Additional information: The mother's obstetrician calls 1 month later. Examination, including sonogram, is normal for her stage of pregnancy. The obstetrician asks you about the potential fetotoxicity of TCE and whether a more invasive evaluation (amniocentesis, chorionic villus biopsy) is indicated. What is your response?

Clinical Evaluation

History and Physical Examination

No unique pattern of symptoms characterizes TCE-induced illness. An occupational history should be routinely obtained and should include items such as company name and location, job title, description of chemical processes encountered, known toxic agents used, workplace investigations, and coworker complaints. An environmental history should also be obtained, including location and duration of residence, proximity to industry, diet, daily activities, type of water supply, and use of consumer products that contain TCE.

☐ **TCE exposure produces no unique clinical clues.**

The patient's complaints should be identified in terms of onset, duration, and intensity. Complaints should be investigated by focusing first on organ systems that are likely to be affected by exposure to TCE (CNS, hepatic, integumentary), and then on systems unlikely to be affected (respiratory, cardiovascular, renal, gastrointestinal, endocrine, skeletal). Patients should receive a complete neurologic examination, including a mental status exam and evaluation of the cranial nerves to detect either peripheral or central nervous system involvement. Cranial neuropathies in patients with a history of TCE exposure, while uncommon, suggest exposure to dichloroacetylene. Presence or absence of an irregular pulse or abnormal cardiac auscultation should be noted. The patient's abdomen should be palpated for hepatomegaly and right upper quadrant tenderness.

Signs and Symptoms

Acute Exposure

☐ **Respiratory depression can result from acute, high-dose TCE exposure.**

With inhalation of high concentrations, TCE causes initial CNS excitation followed by CNS depression. Depending on the duration and intensity of exposure, symptoms may be drowsiness, dizziness, visual disturbances, lightheadedness, fatigue, headache, lethargy, confusion, ataxia, and stupor. Coma and respiratory depression may occur with prolonged, high-level exposure (i.e., above 2000 ppm). Serious ventricular dysrhythmias can develop up to 24 hours after large TCE ingestions.

After any type of acute exposure, the clinician should carefully assess the adequacy of ventilation (respiratory depression is the most common serious sequelae of acute TCE exposure). Because of possible dysrhythmias, patients with preexisting cardiovascular disease should be monitored by continuous ECG and frequent evaluation of vital signs. Since hepatic injury may occur, liver function tests should be performed.

Chronic Exposure

☐ **At permissible workplace levels, CNS symptoms of TCE exposure are usually nonspecific and transient.**

Reported neurologic effects associated with chronic workplace exposure to TCE have included nonspecific symptoms such as headache, ataxia, decreased appetite, sleep disturbances, fatigue, weakness, dizziness, memory loss, emotional instability, impaired judgment. However, study design defects (e.g., exposure data that does not allow for differentiation of acute and chronic effects, failure to analyze confounding variables, lack of controls, and observer bias) limit the conclusion that chronic TCE exposure may cause these effects.

Although CNS symptoms may disappear within several weeks after cessation of exposure, some health effects may persist in persons who have been exposed to TCE for long periods. Persistent neurologic symptoms should also prompt a search for exposure to other potential neurotoxins, such as carbon disulfide, methanol, or n-hexane; drugs of abuse, including alcohol; or psychiatric disorders.

Laboratory Tests

Direct Biologic Indicators

Data are limited for interpreting TCE levels in plasma. Detectable plasma levels of TCE in persons without occupational exposure are approximately 0.01 to 0.13 micrograms per deciliter (μg/dL). Although TCE disappears rapidly from the blood, metabolites (e.g., trichloroacetic acid) may persist in the blood for several weeks and in urine up to 3 weeks after heavy exposure. The presence of TCE metabolites should be interpreted with caution because medications (chloral hydrate, disulfiram) and other chlorinated hydrocarbons (1,1,1-trichloroethane, tetrachloroethylene) are also metabolized to trichloroacetic acid and excreted in the urine. TCE may appear on abdominal X rays as a radiopaque material after ingestion.

☐ **TCE may be measured in the breath and urine up to 16 hours after exposure; metabolites may persist for a week or more.**

☐ **Urinary metabolites are trichloroethanol and trichloroacetic acid.**

Indirect Biologic Indicators

Biochemical abnormalities are uncommon after acute TCE exposures. Rarely have elevations of serum hepatic transaminases (SGOT or AST, SGPT or ALT), bilirubin, and creatinine resulted from acute TCE exposure; nevertheless, liver function and serum creatinine tests should be performed to establish baselines. Electrocardiogram and continuous cardiac monitoring should be considered for heavily exposed persons. Ingestion of large amounts of TCE causing profuse diarrhea may produce an electrolyte imbalance. Because the trigeminal, optic, and facial nerves may be impaired by exposure to dichloroacetylene, changes in the visual fields and trigeminal nerve potentials may be noted.

☐ **Liver function tests, a serum creatinine test, and continuous cardiac monitoring should be considered for persons acutely exposed to TCE.**

Challenge

(7) Additional information for the case study: You evaluate the 4-year-old child. Review of her history reveals three to four episodes of otitis media in each of the last 3 years, which were treated with ampicillin. The child was placed on continuous prophylactic antibiotics during the last two cold seasons. Last year, the child developed additional infections despite the antibiotic regimen, and you referred her to an otolaryngologist, who performed a myringotomy and tympanostomy without incident. The mother estimates the child has had four episodes of coryza or mild influenza last year, with about 7 days of illness that merited staying home from day care.

Does this pattern reflect compromise of the child's immune system?

(8) The mother asks about immune system tests. A health care practitioner evaluating other families has performed such tests. Is the assessment of immunocompetence appropriate in this case?

Treatment and Management

Acute Exposure

In the case of dermal contact with liquid TCE, contaminated clothes should be removed and the affected areas washed with copious amounts of soap and water. Direct eye splashes require irrigation for at least 15 minutes. Corneal epithelium damage usually resolves spontaneously after irrigation.

☐ **Removal from the source and supportive care is the recommended treatment for acute TCE exposure.**

Patients should be removed from the contaminated environment as soon as possible; begin artificial ventilation, if needed. Those with altered mental status or apparent respiratory insufficiency should receive supplemental oxygen. If the patient's pulse is absent, cardiopulmonary resuscitation should be initiated.

Gut decontamination (emesis, lavage, saline cathartic) is recommended if it can be initiated within 2 to 3 hours after ingestion of more than a swallow of TCE. However, the effects of these measures have not been clinically evaluated. If emesis is considered, administer the emetic only to patients who are fully conscious and have an intact gag reflex. Activated charcoal has not been proven to absorb TCE, but in general, effectively decreases absorption of most ingested toxic agents. No data are available on the ability of hemodialysis or hemoperfusion to increase TCE elimination. There are no specific antidotes.

Patients with serious TCE toxicity should be monitored for the possible development of dysrhythmias. When diarrhea is present, monitor for the development of electrolyte abnormalities and screen for the possible development of hepatorenal dysfunction. Sequelae are unusual with acute exposures.

Chronic Exposure

There is no known treatment for chronic exposure to TCE. Potentially involved organ systems should be independently evaluated and supportive measures initiated.

☐ **Symptomatic treatment is recommended for chronic TCE exposure.**

Standards and Regulations

Workplace

Air

☐ **OSHA's current PEL is 50 ppm.**

In 1989, the Occupational Safety and Health Administration (OSHA) lowered the permissible exposure limit (PEL) from a time-weighted average (TWA) of 100 ppm to 50 ppm, with 200 ppm TCE as a short-term exposure limit (STEL). The TWA concentration for a normal 8-hour workday and 40-hour workweek is set at a level at which nearly all workers may be repeatedly exposed without adverse effects. The STEL for TCE is a concentration at which workers can be exposed continuously for a short period of time (usually 15 minutes) without suffering irritation, chronic irreversible tissue damage, or narcosis. NIOSH recommends a 10-hour TWA of 25 ppm. Table 1 summarizes current standards and regulations for TCE exposure.

Table 1. Standards and regulations for trichloroethylene

Agency[*]	Focus	Level	Comments
ACGIH	Air -Workplace	50 ppm	Advisory, TWA[†]
NIOSH	Air -Workplace	25 ppm	Advisory, TWA[†]
OSHA	Air -Workplace	50 ppm	Regulation; PEL[§] over 8-hour workday
		200 ppm	Regulation; STEL[¶]
EPA	Air-Environment	N/A	Under review
	Drinking Water	5 ppb	Regulation

[*] ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration

[†] TWA (Time-Weighted Average) = time-weighted average concentration for a normal 8-hour workday and 40-hour workweek to which nearly all workers may be repeatedly exposed

[§] PEL (Permissible Exposure Limit) = highest level of trichloroethylene in air, averaged over an 8-hour workday, to which a worker may be exposed

[¶] STEL (Short-Term Exposure Limit) = usually determined by a 15-minute sampling period.

Biologic exposure indices are recommended by the American Conference of Governmental Industrial Hygienists and may involve either direct or indirect measures of individual worker exposure. An end-exhaled air sample collected 16 hours after the last TCE exposure (i.e., prior to the next shift) should be 0.4 ppm or less. Free trichloroethanol in the blood may be measured, but a number of other compounds affect the level of trichloroethanol and must be considered as alternate explanations for elevated levels.

Alternatively, a concentration of 100 milligrams (mg) of trichloroacetic acid per liter (L) of urine at the end of the work week reflects the upper biologic limit for TCE exposure. Urinary trichloroacetic acid levels can be increased by the same compounds that affect blood trichloroethanol levels. Because of large individual variations, this urinary trichloroacetic acid level of 100 mg/L should be used only as a "warning" level or mean for a group of workers.

Environment

Environmental exposures to TCE are generally low and are decreasing since limitations have been imposed on its use as an anesthetic, solvent extractant, fumigant, and dry-cleaning agent. TCE has a short atmospheric half-life (less than 7 days) and does not accumulate in the food chain. The World Health Organization recommended drinking water limit is 30 µg TCE/L of water (30 ppb); EPA recommends a maximum contaminant level of 5 µg/L (5 ppb) in drinking water. Based on the available data, no known human health effects are associated with exposures to environmental levels of TCE, but more comprehensive information is necessary for a final assessment.

Challenge

(9) TCE has been identified as the irritant at the day-care center. The mother described in the case study is concerned and wishes to take action to get the level reduced. What can you recommend to her?

Suggested Reading List

General

Fan AM. Trichloroethylene: water contamination and health risk assessment. Rev Environ Contam Toxicol 1988;101:55-92.

Feldman RG, White RF, Currie JN, Travers PH, Lessell S. Long-term follow-up after single toxic exposure to trichloroethylene. Am J Ind Med 1985;8:119-26.

International Agency for Research on Cancer: IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, Suppl 7. Trichloroethylene. Lyons, France: World Health Organization, 1987.

International Programme on Chemical Safety: Environmental Health Criteria 50 Trichloroethylene, Geneva: World Health Organization, 1985.

Kimbrough RD, Mitchell FL, Houk VN. Trichloroethylene: an update. J Toxicol Environ Health 1985;15: 369-83.

Shindell S, Ulrich S. A cohort study of employees of a manufacturing plant using trichloroethylene. J Occup Med 1985;27:577-9.

Smith GF. Trichloroethylene: a review. Br J Ind Med 1966;23:249-62.

Tola S, Vilhunen R, Jarvinen E, Korkala ML. A cohort study on workers exposed to trichloroethylene. J Occup Med 1980;22:737-40.

Specific Health Effects

Adams RM. Degreaser's flush. West J Med 1976;125:487.

Forkert PG, Sylvestre PL, Poland JS. Lung injury induced by trichloroethylene. Toxicology 1985; 35: 143-60.

King GS, Smialek JE, Troutmen WG. Sudden death in adolescents resulting from the inhalation of typewriter correction fluid. JAMA 1985;253:1604-6.

Lawrence WH, Partyka EK. Chronic dysphagia and trigeminal anesthesia after trichloroethylene exposure. Ann Intern Med 1981;95:710.

Related Government Publications

Agency for Toxic Substances and Disease Registry. Toxicological profile for trichloroethylene. Atlanta: US Department of Health and Human Services, Public Health Service, 1989. NTIS report no. PB/90/127523/AS.

Environmental Protection Agency. Health assessment document for trichloroethylene. Final report. Washington, DC: EPA, 1985. NTIS report no. PB/85-249696.

Environmental Protection Agency. Addendum to the health assessment document for trichloroethylene: update carcinogenicity assessment for trichloroethylene. Review draft. June 1987. Report No. EPA/600/8-82/006FA.

Answers to Pretest and Challenge Questions

Pretest

Pretest is found on page 1.

(a) The mother's problem list includes pregnancy and anxiety; and the child's, frequent otitis media (status post myringotomy and tympanostomy tube placement) and frequent upper respiratory infections.

(b) You will need information on TCE toxicity, including reproductive and developmental effects; information on TCE contamination of the family's drinking water, including duration of contamination; copies of information provided to the family by the municipal water company; and responses, if any, from local and state health agencies.

(c) None of the symptoms described in the case indicates serious illness. However, you should reassure the family that you will perform complete physical examinations with appropriate testing at the next visit. In response to concern about the child's infections, you should indicate that you will collect information about possible TCE effects on the immune system. Explain to the parents that tests of immune function are often difficult to interpret and may not be appropriate. You may indicate that you will consult sources of information on TCE's effects on pregnancy. It is important to maintain a balance between reassurance that the unborn child is probably not affected by the water contamination and concern for the possible risk to the fetus. Reassurance should not, however, appear to trivialize the family's fears. It would also be appropriate to discuss that no evaluation, however thorough, can totally exclude the possibility that a person may develop an illness, including cancer.

Challenge

Challenge questions begin on page 4.

(1) Possible sources of the family's TCE exposure include home drinking water (dermal and inhalation exposure during bathing, and ingestion), father's workplace (inhalation), and the daughter's day-care center (inhalation). Minor sources might be certain foods such as margarine (ingestion) and use of TCE-containing consumer products such as correction fluid, spot removers, etc. (inhalation).

(2) From the information about the family thus far, none of them fits the profile of a person at increased risk from the effects of TCE exposure. That is, there is no indication that any family member has liver dysfunction or cardiac disorders, abuses TCE, or consumes large amounts of alcohol.

(3) The most convenient biologic indicators of TCE exposure are the urinary metabolites, trichloroethanol and trichloroacetic acid. These metabolites are not specific to TCE, however, since they are also metabolites of tetrachloroethylene (perchloroethylene) and 1,1,1-trichloroethane (methyl chloroform) and certain medications. TCE itself can be measured directly in blood or exhaled air, but because of the difficulty of obtaining samples, such measurements are not indicated here.

(4) To properly interpret any of the tests mentioned in (3), a knowledge of the time-lapse between exposure and collection is necessary. To prevent contamination or sample loss (evaporation, adsorption), the proper collection, handling, storage, and transportation procedures must be followed. It is unlikely that any member of this family would have levels of TCE or its metabolites significantly above background levels. Furthermore, there are no appropriate reference values currently available for a health risk assessment.

(5) No further studies are indicated for TCE exposure. A workup for fatigue may indicate additional tests.

(6) Based on limited evidence from animal studies, researchers believe teratogenicity does not occur at environmental TCE levels. Invasive procedures are not justified on the basis of the drinking water contamination.

(7) No, a recent survey of infections in children under 3 years of age over a September to March period found an average of 2.5 total infections and more than one episode of otitis media per child (1.4 episodes per child for those in day care). Over 3% of the children in day care were hospitalized for tympanostomies. (Reference: Bell DM, Gleiber DW, Mercer AA, et al. Illness associated with child day care: a study of incidence and cost. Am J Public Health 1989;79:479-84.) The child described in the case study appears to have an above-average rate of infections, but they are not frequent enough to suggest immunologic impairment.

(8) No, immunocompetence tests are not appropriate because no evidence of immune function abnormalities has been found in similar situations. Nevertheless, physicians may be asked to explain further why they are not performing the tests on their patients. Two references that may be of value are (1) Kahn E, Letz G. Clinical ecology:environmental medicine or unsubstantiated theory? Ann Intern Med 1989; 2:104-6; and (2) American College of Physicians. Clinical ecology. Ann Intern Med 1989;2:168-78.

If it had been indicated, laboratory evaluation of immunologic host-defense defects would consist of three phases. The preliminary screening is a complete blood count with differential smear and quantitative immunoglobulin levels. These tests, together with history and physical examination, will identify more than 95% of patients with primary immunodeficiencies. The second phase of testing consists of readily available studies including B-cell function (such as antibodies, response to immunization), T-cell function (skin tests, contact sensitization), and complement levels. The first two phases combined will detect most immunodeficiencies amenable to conventional treatment with gamma globulin or plasma. The third phase (in-depth investigation) consists of testing induction of B lymphocyte differentiation in vitro, stimulated by pokeweed mitogen and histologic and immunofluorescent examination of biopsy specimens; T-cell surface markers; assays of T-cell helper or killer cell functions; and functional assays using appropriate target cells. It is inappropriate to perform these latter tests on environmentally exposed patients except for epidemiologic research.

Primary immunodeficiency is suspected in an infant who has repeated upper respiratory tract or other infections. It is also suspected if repeated infection occurs in a child who has had little exposure to infectious agents, or any child with unusual infections, incomplete clearing of infections, growth failure, hepatosplenomegaly, or features associated with specific immunodeficiency disorders, such as ataxia or telangiectasia. The child described in the case study has none of these indications.

(9) EPA has not issued an emission standard for TCE. Assuming discussions with the owner or operator of the shop adjacent to the day-care center have not been effective in reducing the level of ambient TCE, the community's air pollution control center should be notified. States may allow this control under the jurisdiction of local air pollution control districts, county health departments, or other local agencies. The agency responsible for enforcement of air standards should be contacted to investigate possible release of TCE onto the day-care center property.

ATSDR June 1990

Case Studies in Environmental Medicine

2

Vinyl Chloride Toxicity

Environmental ALERT . . .

☑ ***Chronic, low-level vinyl chloride exposure may cause angiosarcoma of the liver, an extremely rare form of cancer.***

☑ ***At higher doses, hepatic cells may die rather than transform, which results in chronic liver disease.***

☑ ***Hepatic angiosarcoma has not been reported in workers who were exposed to vinyl chloride after 1974, when permissible workplace air levels were drastically reduced. This finding, however, may reflect an incomplete latency period.***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. The Agency for Toxic Substances and Disease Registry (ATSDR) and the Centers for Disease Control (CDC) designate this continuing medical education activity for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association and 0.1 continuing education units for other health professionals. See pages 19 to 21 for further information.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

A 55-year-old man with weight loss and hepatomegaly

A 55-year-old man seen at your office complains of fatigue, a 20-pound weight loss, and anorexia over the past 2 to 3 months. He has previously been in good health, except for a history of hypertension, for which he has been treated with hydrochlorothiazide, 50 mg a day, for the past 3 years. He takes no other medications, has never had a blood transfusion, and has not travelled outside the United States. He consumes 2 to 3 alcoholic beverages a week and does not smoke tobacco.

Questioning reveals that he has been a car salesman for 25 years. He is married, has 3 children, and has lived near an industrial park for the last 18 years. Three and a half years ago, he and his family were evacuated from their home for several days after a railroad tanker car derailed and ruptured on the nearby railroad tracks. He and his family were treated at a local emergency room for sore throat and cough; acute respiratory complaints resolved within 2 weeks. He does not recall the name of the chemical that was released, but he remembers it had a slightly sweet odor, an odor he has occasionally noticed while in the backyard. His youngest daughter, who has just turned 19, gave birth to a boy last week; the pregnancy was troubled, but the baby is fine. The rest of his family is in good health.

On physical examination, your patient appears to be in poor health. Blood pressure is 140/80; pulse is 72 and regular. He is afebrile. Weight is 174 pounds. There are no skin rashes or lesions. Sclerae are slightly icteric; the remainder of the HEENT examination is normal. There is no thyromegaly or lymphadenopathy. The results of heart and chest examination are normal. The patient's liver is 14 cm in span, percusses at the midclavicular line, and is slightly tender to palpation; the lower border is palpable 4 cm below the costal margin. The spleen is not enlarged, and there are no other abdominal masses. Extremities and joints are unremarkable, and the results of neurologic examination are completely normal. Prostate is normal-sized; no masses are felt, and the stool is negative for occult blood.

The initial laboratory results include hemoglobin, white blood cell count, electrolytes, and urinalysis, all normal. The SGPT is 372 IU/L and SGOT is 293 IU/L. Bilirubin, alkaline phosphatase, and serum protein levels are within normal limits.

Pretest

(a) *What should be included in this patient's problem list?*

(b) *What is the differential diagnosis for this patient?*

(c) *What tests would you crder to confirm or rule out these diagnoses?*

Answers are incorporated in Challenge answers (6) through (9) on pages 17-18.

Exposure Pathways

- ☐ **The sweet odor of vinyl chloride can be detected only at concentrations too high to provide adequate warning of toxic levels.**
- ☐ **Exposures may occur through air polluted with vinyl chloride from processing, polymerization, and fabrication plants or hazardous waste sites, and through groundwater contaminated by these sources.**
- ☐ **Consumer sources of vinyl chloride may include release of the monomer from PVC plastic in new car interiors, packaging of certain foods and beverages, and pipes for drinking water.**

Vinyl chloride (CH_2=CHCl) is a manmade chemical with no significant natural source. It is a colorless gas at room temperature but is normally stored under pressure and used as a liquid. It has a mild, sweet odor that can be detected at 300 to 5000 parts per million (ppm), too high to provide adequate warning of danger. Vinyl chloride is soluble in fats and organic solvents and is only slightly soluble in water. Synonyms include chloroethene, monochloroethylene, VC, and VCM (vinyl chloride monomer). Throughout the text, "vinyl chloride" refers to the vinyl chloride monomer, unless otherwise stated.

The primary use of vinyl chloride is in the production of polyvinyl chloride (PVC), a plastic that is used to make pipe, electrical wire and cable coatings, flooring, home furnishings, toys, packaging, apparel, and automobile parts and upholstery. Smaller amounts of vinyl chloride are used as a copolymer in the manufacture of other plastics, as an intermediate in the production of chlorinated compounds, and as a refrigerant. Historically, vinyl chloride has been used as an aerosol propellant and, at one time, was considered for use as an anesthetic.

Normally, the general population is exposed to negligible amounts of vinyl chloride. Amounts measured in ambient air near vinyl chloride production plants have been up to 1 ppm and, above hazardous waste sites, up to 0.4 ppm. Other sources of airborne exposure include volatilization from new plastic parts and upholstery in car interiors. Release of residual vinyl chloride monomer from most other solid PVC materials is generally of little consequence, although significant amounts of vinyl chloride may be released during burning of PVC products. Tobacco smoke also contains small amounts of vinyl chloride. In general, atmospheric environmental levels of vinyl chloride are not injurious and present no known risk.

Many consumer goods, including food and beverages, are packaged in various forms of polyvinyl chloride. Small amounts of residual vinyl chloride monomer can migrate into the packaged contents and be consumed. Residual monomer can also be leached into the drinking water supply from new PVC piping. Studies have shown, however, that the amount of vinyl chloride ingested from either of these sources is small.

Vinyl chloride released from point sources into the ambient air is degraded in a matter of hours; that released to lakes, streams, or rivers will volatilize in several hours to days, depending on the water's temperature and aeration rate. Vinyl chloride may remain in groundwater, however, for months or years. Of all potential sources of vinyl chloride exposure to the general population today, contaminated groundwater is the most enduring. The majority of drinking water supplies in the United States contain no detectable amounts of vinyl chloride.

Challenge

(1) Additional information for the case study: After checking with the local fire department, you find that vinyl chloride was contained in the overturned tanker car and that there was an airborne release of approximately 10,000 gallons of vinyl chloride. Furthermore, you learn from the regional office of EPA that significant leaks in the reactor vessels of the nearby plant may have been occurring over the course of several decades, resulting in frequent environmental contamination, although no air monitoring had been done outside the plant. After the tanker car accident, the complex permanently closed. What further information will you request in order to evaluate the extent of your patient's exposure?

(2) What are the significant sources of vinyl chloride exposure for this patient?

Who's at Risk

Those at greatest risk of vinyl chloride exposure are the 2.2 million workers concerned with the production, use, transport, storage, and disposal of this material. The highest health risk has been to workers exposed as a result of the polymerization process, especially to those who were lowered directly into the reactor vessels to remove solid polymer adhering to the inside. During this cleaning process, the exposure levels to vinyl chloride monomer were typically in the range of 100 ppm or more.

☐ **Of the 2.2 million workers exposed to vinyl chloride, autoclave cleaners in PVC production plants have the highest health risk.**

- ☐ **Certain persons, such as alcoholics, have an increased risk of vinyl chloride toxicity.**
- ☐ **During the childbearing years, women should avoid exposure since there is a possibility that vinyl chloride increases the incidence of congenital birth defects.**
- ☐ **Prenatal or early exposure to vinyl chloride may increase the risk of cancer later.**

Data from animal studies suggest that prior exposure to chemicals or drugs that stimulate the enzyme systems involved in vinyl chloride hepatic metabolism may result in increased risk of hepatotoxicity. The formation of scar tissue, which results from vinyl chloride-induced chronic liver disease, has been reported to cause hepatomas that can become malignant when ethanol is consumed.

The fetus may also be at increased risk. One human study suggests that maternal exposure to low ambient levels of vinyl chloride is associated with an increase in the incidence of congenital malformations, but these results have not been supported by the findings of at least two subsequent studies. Based on extrapolation of animal data, exposure to vinyl chloride either in the prenatal period or during early childhood years may result in an increased risk of developing cancer.

Challenge

(3) Who in the case study, besides the patient, is at risk of being exposed to vinyl chloride?

(4) Do the children of this patient have an increased risk of developing cancer? Does his grandson? Why?

Biologic Fate

- ☐ **Primary routes of vinyl chloride entry in humans are inhalation and ingestion.**

For vinyl chloride, the primary routes of entry in humans are inhalation and ingestion. Metabolic pathways are readily saturable, which limits systemic uptake at higher doses. Vinyl chloride that is not metabolized is exhaled.

Animal studies indicate that inhalation absorption of vinyl chloride occurs readily and rapidly, but data are insufficient to determine the proportion of an inhaled dose that is absorbed. Absorption from the gastrointestinal tract is rapid and probably complete, as shown by several studies performed on rats.

Evidence suggests that the toxicity of vinyl chloride is related to its transformation in the liver to one or several reactive metabolite(s). Suspected intermediate metabolites, 2-chloroethylene oxide and 2-chloroacetaldehyde, can bind to cellular macromolecules such as DNA and proteins, presumably causing liver damage. These metabolites can also undergo further oxidation to compounds such as 2-chloroacetic acid and thiodiglycolic acid, which are mainly excreted in the urine.

☐ **Following absorption, vinyl chloride is metabolized in the liver. The primary metabolites can cause cellular damage or be further metabolized to compounds that are excreted in the urine.**

Physiologic Effects

Acute Exposure

Most data regarding acute inhalation exposure to vinyl chloride are early reports among occupationally exposed workers. Deaths appeared to be due to narcosis, but no specific exposure levels have been reported. Presumably, these exposure levels exceeded 10,000 ppm. Autopsies revealed congestion of the liver, spleen, and kidneys.

☐ **With acute exposure to vinyl chloride, the nervous system is the primary target.**

Chronic Exposure

Several epidemiologic studies have convincingly associated chronic vinyl chloride exposure with liver tumors, both malignant and nonmalignant, and have suggested, but not proved, an increased incidence of cancers in other parts of the body. Subtle neurologic effects have been noted in some workers chronically exposed to vinyl chloride. Vinyl chloride exposure also has been associated with decreases in pulmonary flow, interstitial pneumonitis, and "meat packers' asthma."

☐ **With subacute or chronic exposure, the primary target organ is the liver.**

Hepatic Effects

☐ **Vinyl chloride can cause malignant or nonmalignant liver injury, depending on exposure level.**

Hepatocellular injury of any kind is manifested only after months or years of vinyl chloride exposure. Epidemiologic studies suggest that chronic exposure to very high doses (on the order of 500 to 1000 ppm) leads more often to hepatotoxicity, while exposure to lower doses (100 ppm or less) results more often in carcinogenicity. At the higher levels hepatic cells often die rather than transform, which results in chronic liver disease.

Hepatic angiosarcoma is a multicentric lesion that typically occupies peripheral foci within the liver. The highly vascular nature of angiosarcomas causes the bruits and may result in massive peritoneal hemorrhage. Nonmalignant hepatic manifestations of vinyl chloride exposure include noncirrhotic portal hypertension and cirrhosis, depending on the nature of exposure. In cases of acute exposure, the resulting chemical hepatitis rarely progresses into fulminant hepatic necrosis. Chronic exposure results in periportal fibrosis without portal vein obstruction, collagen deposition in the space of Disse, and hyperplasia of the mesenchymal sinusoidal lining cells, which ultimately become fibrotic. Vinyl chloride exposure should be considered before the diagnosis of idiopathic portal hypertension is made. Exposure to arsenic, thorium, and copper may also cause portal hypertension without cirrhosis. Findings of capsular and subcapsular fibrosis are suggestive but not diagnostic of vinyl chloride exposure.

Neurologic Effects

☐ **Subtle signs of neurotoxicity have recently been associated with chronic exposure to vinyl chloride.**

Vinyl chloride was once considered for use as an inhalation anesthetic agent, a result of its central nervous system effects at subacute exposures. Recent data suggest that more subtle signs of neurotoxicity can be associated with chronic exposure. Peripheral neuropathy of the legs has been reported in workers exposed to vinyl chloride at levels less than 50 ppm. Electroencephalographic changes have been noted in workers chronically exposed to vinyl chloride at high levels and in combination with other organic solvents. Further investigation in this area is needed.

Carcinogenic Effects

☐ **Vinyl chloride-induced angiosarcoma of the liver has a reported latency of 15 to 40 years.**

Numerous epidemiologic and experimental studies have indicated the carcinogenic potential of vinyl chloride. A worldwide register of histologically confirmed cases of hepatic angiosarcoma resulting from vinyl chloride exposure identified 120 cases from 1974 to 1986; additional cases are now being added at the rate of about 5 a year.

Most of these cases were found 15 to 29 years after first exposure; the mean age of patients at diagnosis was 52 years, and the average length of exposure was 18.3 years. As of 1986, at least 43% (53/120) of the people with this rare form of cancer were employed as reactor cleaners; exposure levels then were presumably much greater than those seen today. Most of the workplace cases of vinyl chloride-induced hepatic angiosarcoma have been associated with chronic exposures on the order of 100 ppm or less; evidence for increased incidence of disease below 50 ppm has not been clearly documented in human studies.

There have been no cases of hepatic angiosarcoma recorded in workers due to vinyl chloride exposure after 1974, when allowable workplace air levels were drastically reduced. However, a sufficient latency period has not yet elapsed for carcinogenic effects to have appeared. Data on the few cases of hepatic angiosarcoma reportedly due to environmental contamination are inconclusive because of the statistically small numbers involved and because this disease can arise spontaneously.

Increased incidence of several cancers, other than hepatic, have been suggested by various epidemiologic studies of vinyl chloride-exposed workers and by animal studies. Presently, there is insufficient evidence to establish a causal relationship in humans between environmental vinyl chloride exposures and suggested increased incidences of cancer of the brain, breast, skin, lung, thyroid, lymphatic, or hematopoietic tissues.

Increased frequencies of chromosomal aberrations in circulating peripheral lymphocytes, including fragments, rings, breaks, and gaps, have been reported in vinyl chloride workers. In general, these aberrations have not been associated with exposure to vinyl chloride levels less than 5 ppm. Studies using a number of biologic assay systems suggest that the reported carcinogenicity of vinyl chloride may proceed by damage to the cell's genetic material.

Challenge

(5) Would you examine the patient described in the case study for CNS damage? For malignancies other than hepatic? Explain.

Clinical Evaluation

History and Physical Examination

☐ **The onset of symptoms due to chronic vinyl chloride exposure may be delayed for several years after the actual exposure has ceased.**

A detailed occupational history should include any past exposure to vinyl chloride. The latency period for nonmalignant complications may be several months, while the latency period for angiosarcoma of the liver may be as long as 40 years. Workers exposed before 1974, when permissible workplace levels were still high, are at increased risk for the development of hepatic angiosarcoma into the next century. Individual susceptibility as well as intensity and duration of exposure may affect the interval before symptoms are manifested.

Persons who have been chronically exposed to vinyl chloride are likely to have worked or lived in locations where the chemical was produced, used, or stored. Such proximity to vinyl chloride plants operating before 1960, when engineering controls were inadequate, is particularly suspect. Although the number of symptomatic persons having this type of exposure is small, angiosarcoma of the liver is so rare that the incidence of even.one case near such a plant may be initially regarded as evidence of environmental pollution. Documentation of environmental contamination, in air or drinking water, would suggest a need to monitor other potentially exposed members of the community, past and present residents, and workers connected with the source of exposure.

Two other chemical agents have been specifically associated with angiosarcoma of the liver, and exposure to them should be ruled out by history; these are inorganic arsenic and thorium dioxide (a component of the X-ray contrast medium Thorotrast). Anabolic and contraceptive steroids have also been associated with the induction of hepatic angiosarcoma, and their use should be determined. In addition to alcohol consumption and smoking habits, any medications that normally or adversely affect the liver should be noted. The possible use of homeopathic medications and so-called health foods should be investigated.

The physical examination for vinyl chloride-exposed persons includes a thorough abdominal and neurologic examination. The extremities of vinyl chloride workers, particularly the hands, should be examined for signs of acro-osteolysis, a result of "vinyl chloride disease," discussed in Signs and Symptoms section.

Signs and Symptoms

Acute Exposure

Vinyl chloride has little acute toxicity, and air levels over 8000 ppm may be tolerated for 5 minutes without the development of symptoms. Longer exposures have been associated with headache, dizziness, euphoria, ataxia, and narcosis. Cardiac, circulatory, and respiratory irregularities have also been noted with acute exposures. Acute, high-level exposures have resulted in death, presumably due to narcosis.

- **Short-term vinyl chloride exposure at relatively high concentrations may be tolerated without lasting adverse effects.**

Chronic Exposure

Chronic occupational exposures to vinyl chloride at levels of several hundred ppm have led, in the past, to vinyl chloride disease, a condition involving a number of organ systems and tissues and resulting in a variety of clinical symptoms. The reported period of exposure before the onset of this disease ranged from 1 month to 3 years. New cases of vinyl chloride disease have not been reported since 1974, when permissible workplace exposure levels were reduced to 1 ppm.

- **Vinyl chloride disease appears to be a disease of the past.**
- **The onset of vinyl chloride-induced liver damage is insidious, with a clinical picture of nonspecific hepatic injury.**

The signs of vinyl chloride disease included a scleroderma-like condition of the connective tissue of the fingers, accompanied by thickening of the dermis. Acro-osteolysis, a rare bone disease resulting in decalcification of the terminal phalanges of the hand, was also seen. Acro-osteolysis was frequently preceded by a Raynaud-type phenomenon in which there was reversible constriction of the arterioles, leading to numbness, pallor, and cyanosis of the fingers.

The onset of vinyl chloride-induced liver disease (malignant or nonmalignant) can be insidious, with a clinical picture of nonspecific hepatic injury. Abdominal pain, followed by weakness, fatigue, and weight loss are the most common symptoms. Fibrosis and cirrhosis may develop, resulting in hepatomegaly, splenomegaly, portal hypertension, thrombocytopenia, and esophageal varices. These pathologic effects may occur singly or in any combination and may be accompanied by other less characteristic signs, such as hematologic changes and pulmonary effects.

Laboratory Tests

☐ **In the evaluation of vinyl chloride-exposed patients, it is important to exclude other etiologies for liver disease.**

Short of liver biopsy, there are no definitive clinical clues to distinguish hepatic injury due to vinyl chloride from that of other etiologies such as viral hepatitis infection and ethanol toxicity. (Vitamin A overload, hemochromotosis, and carbon tetrachloride exposure have been reported to cause liver disease only rarely.) Biliary cirrhosis, cholelithiasis, and metastatic cancer should also be considered in the differential diagnosis of liver injury.

Laboratory tests can be used to evaluate patient health, confirm vinyl chloride exposure, and exclude other etiologies such as hepatitis virus. Tests that may be helpful are listed below. Since the histologic appearance of vinyl chloride-induced liver injury is distinct from that due to other agents, biopsy may be the best method to diagnose liver disease caused by this chemical.

Screening Tests

Urinary coproporphyrin and total urinary porphyrins
Liver enzymes
Liver function tests (see below)
Serum bilirubin
CBC with peripheral smear
BUN and creatinine
Urinalysis
Hepatitis serology

Specialized Tests

Vinyl chloride in breath or urine, if exposure is recent
Urinary thiodiglycolic acid, if exposure is recent

Direct Biologic Indicators

☐ **There is no reliable direct indicator for vinyl chloride exposure at low levels.**

No reliable direct method exists for biologically monitoring exposure to low levels of vinyl chloride. Attempts have been made to correlate vinyl chloride exposure with urinary output of thiodiglycolic acid, a major urinary metabolite that peaks approximately 20 hours after exposure. Because of wide individual variations in excretion patterns, however, urinary thiodiglycolic acid is not reliable when exposure to vinyl chloride occurs at concentrations less than 5 ppm nor several days after exposure. Likewise, at air concentrations less than 5 ppm, no correlation has been found between the amount of vinyl chloride in breath or urine samples and the concentration in inspired air.

Indirect Biologic Indicators

Overt liver injury is a relatively late occurrence in vinyl chloride-related hepatic disease, and detection of early chemical injury in asymptomatic persons is difficult. Standard biochemical enzyme studies (alkaline phosphatase , aspartate aminotransferase [SGOT or AST], alanine aminotransferase [SGPT or ALT] and gamma-glutamyl transpeptidase [GGTP or GGT]), when used alone, are of limited value in identifying the early phases or progression of liver injury. These enzymes primarily reflect acute disruption in cell membrane integrity rather than alterations in the uptake, metabolism, storage, or excretion functions of hepatic cells. Furthermore, these enzyme levels may be elevated in nonhepatic diseases or may return to normal after initial elevation in subacute, chronic, or end-stage liver disease, thus complicating their interpretation.

A correlation has been noted between slightly to moderately elevated total urinary porphyrins or secondary urinary coproporphyrin and the early stages of toxic liver disease. However, no similar observations have been reported in patients with vinyl chloride-related liver disease.

Recent studies have suggested that measuring clearance rates of substances removed from the circulation by the liver provides the most sensitive and specific indicator of early chemically induced liver injury. Indocyanine green (ICG) is a synthetic dye used for this purpose, and ICG clearance rates are directly related to the severity of chemical hepatic injury. This test, however, has certain limitations: it is invasive, involves intravenous injection of a synthetic dye, necessitates drawing multiple blood samples with same-day analysis, and is fairly expensive.

Serum bile acids are also cleared by the liver; measurement requires drawing a single fasting serum sample to obtain levels, usually by radioimmunoassay. These bile acids, cholylglycine and conjugates of cholic acid, have been shown to be significantly elevated in asymptomatic workers with chemical exposure and histologically proven chemical liver injury.

A screening panel of fasting serum bile acids and liver enzyme assays or ICG clearance rates is both sensitive (few false negatives) and specific (few false positives) for chemically induced hepatic injury. In asymptomatic persons, the presence of elevated liver

- ☐ **Except in an ongoing medical surveillance program, standard biochemical and liver function tests alone may be of limited value in evaluating vinyl chloride-induced liver injury.**
- ☐ **A rise in urinary coproporphyrin and total urinary porphyrins can signal the early stages of hepatocellular disease.**
- ☐ **Recent studies suggest that fasting serum bile acids, in conjunction with an indocyanine green clearance rate, are sensitive and specific for latent chemical liver injury.**

enzymes or abnormal ICG clearance rates, in conjunction with normal bile acids, is characteristic of hepatic cellular injury due to alcohol, drugs, or viral hepatitis. On the other hand, elevated fasting serum bile acids, in conjunction with persistent enzyme abnormalities or elevated ICG clearance rates, are more indicative of subclinical hepatic injury due to low-grade chemical exposure. When serum bile acids, alkaline phosphatase, and SGPT (ALT) are all normal, there is a high probability of excluding latent liver disease due to any cause; only a liver biopsy is more definitive.

Challenge

(6) What should be included in the problem list for the patient described in the case study?

(7) What is the differential diagnosis?

(8) What additional diagnostic tests should be performed to restrict the differential diagnosis?

(9) Additional information: Hepatitis A antibody is negative, as are hepatitis B core antibody and antigen and surface antigen. What is included in the differential diagnosis now?

Treatment and Management

Acute Exposure

After acute vinyl chloride exposure, the patient should be immediately removed from the source and given oxygen, if indicated. Any persistent effects should be treated symptomatically. Recovery from acute effects is usually rapid and complete with supportive therapy; there is no specific treatment or antidote for vinyl chloride exposure.

☐ **There is no specific treatment for patients with acute exposure to vinyl chloride.**

Chronic Exposure

In the past, symptoms associated with vinyl chloride disease tended to disappear within 1 or 2 years after the patient was removed from exposure. Hepatic angiosarcoma, on the other hand, grows rapidly and carries a poor prognosis; if untreated, most patients die within 6 to 12 months of diagnosis. Results of radiation therapy and chemotherapy have been disappointing. Patients who have had the tumor successfully resected have experienced long-term survival. Patients with chronic liver injury should avoid alcoholic beverages, tobacco use, and exposure to vinyl chloride, acetominophen, isoniazide, or other hepatotoxins. Follow-up may require treatment for complications such as ascites, diabetes, and bleeding varices.

☐ **Unlike vinyl chloride disease, hepatic angiosarcoma has a poor prognosis.**

Challenge

(10) What can you tell the patient described in the case study about hepatic angiosarcoma? How will you advise him?

(11) What is the danger to other members of your patient's family and the community? What tests could you use to evaluate and monitor these persons?

Standards and Regulations

The table below summarizes the standards and regulations for vinyl chloride, which are then discussed in greater detail.

Table 1. Standards and regulations for vinyl chloride

Agency[*]	Focus	Level	Comments
ACGIH	Air-Workplace	5 ppm	Advisory; TWA[†], confirmed human carcinogen
		10 ppm	Advisory; short-term limit, averaged over 15 minutes
NIOSH	Air-Workplace	0	Advisory; zero exposure because of carcinogenicity
OSHA	Air-Workplace	1 ppm 5 ppm	Regulation; PEL[§] over 8-hour workday Regulation; short-term limit not to exceed 15 minutes
EPA	Air-Environment	10 ppm	Regulation; emission limit
EPA	Water	2 μg/L	Regulation; effective January 9, 1989, for all water systems that regularly serve the same 25 persons at least 8 months/year
FDA	Food	5-50 ppm	Proposal; monomer content of polymers used in food packaging or processing

[*] ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration

[†] TWA (Time-Weighted Average) = time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek to which nearly all workers may be repeatedly exposed.

[§] PEL (Permissible Exposure Limit) = highest level of vinyl chloride in air, averaged over an 8-hour workday, to which a worker may be exposed.

Workplace

Air

☐ **The PEL set by OSHA is 1 ppm averaged over an 8-hour workday.**

The Occupational Safety and Health Administration (OSHA) requires that a worker's exposure to airborne vinyl chloride monomer not exceed 1 ppm averaged over any 8-hour period and that a worker not be exposed to greater than 5 ppm for any period of time exceeding 15 minutes. Direct contact with the liquid is prohibited.

The American Conference of Governmental Industrial Hygienists recommends an exposure limit of 5 ppm for an 8-hour day and a short-term exposure limit of 10 ppm. The National Institute for Occupational Safety and Health (NIOSH) has concluded that an exposure level for vinyl chloride is inappropriate because of its carcinogenicity. NIOSH has recommended that workers exposed to vinyl chloride wear an air-supplied respirator.

☐ **NIOSH recommends a zero exposure limit for vinyl chloride.**

Environment

Air

The 1982 EPA emission standards for chemicals released to the atmosphere set a limit for vinyl chloride of 10 ppm, measured at the source.

☐ **EPA has set an emission standard of 10 ppm for vinyl chloride.**

Water

Pursuant to the Safe Drinking Water Act, EPA has issued a maximum contaminant level for vinyl chloride of 2 micrograms per liter (µg/L) or 2 parts per billion (ppb), effective January 9, 1989. This regulation applies to all community drinking water systems that regularly serve the same 25 persons for at least 8 months of the year.

☐ **The maximum contaminant level for vinyl chloride in drinking water is 2 ppb.**

Food

The Food and Drug Administration (FDA) proposed in 1986 that the vinyl chloride monomer content of polymers used in food packaging or processing be limited to 5 to 50 ppm, depending on the nature of the polymer and its use. These levels would produce negligible amounts of vinyl chloride in the food.

☐ **FDA limits the content of vinyl chloride monomer in PVC that is used for food packaging.**

Challenge

(12) Where would you get help in order to evaluate others living or working in the community near the former vinyl chloride facility and the workers who were employed at the plant?

Suggested Reading List

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Related Government Documents

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Answers to Pretest and Challenge Questions

Pretest questions are found on page 1. Challenge questions begin on page 3.

(1) Since the odor of vinyl chloride was detected by your patient, you can conclude that the air concentration must have been high (300 to 5000 ppm) and that your patient received toxic doses on those occasions. You may want to determine if others smelled the vinyl chloride. In cases where plant records are available, it is desirable to obtain the frequency and extent of contamination from them. The drinking water in your patient's home should be tested since groundwater contamination, caused by a release from the plant, is a possibility.

(2) In addition to exposure through possible contamination of the air and water at home, your patient may be exposed to vinyl chloride at work. As a car salesman, he may daily spend time inside new cars where the ambient air can contain significant amounts of vinyl chloride (1 to 10 ppm) released from plastic and upholstery, including the dashboard and seats. To the general population, this and other sources of consumer exposures to the monomer such as PVC food packaging and flooring are of little concern.

(3) Those closest to the source of vinyl chloride, i.e., the former workers at the plant, are at highest risk. Assuming only air emissions from the plant, your patient's immediate family, the surrounding community, and especially those residents immediately downwind have probably been periodically exposed. Since airborne vinyl chloride normally photodegrades within a few hours, ambient air exposure is likely to occur only a limited distance from the plant. If the groundwater has been contaminated, on the other hand, the number of persons affected could be far greater, and they could be located at some distance from the plant.

(4) Your patient has lived near the vinyl chloride plant for 18 years. His children may have been periodically exposed in their younger years, depending on their ages. Data from animal studies suggest that exposure at an early age may increase the risk of cancer later; however, there is no supportive human evidence. The patient's grandson has not been exposed to contaminated air because the plant shut down 2 years ago. There is no evidence that vinyl-chloride contaminated water would have any effect on the child, pre- or postnatally.

(5) Yes. It would be prudent to investigate all potentially involved organ systems, although there is no conclusive evidence that environmental exposures to vinyl chloride result in neurotoxicity or cancers other than hepatic.

(6) The patient's problem list includes fatigue, weight loss, and liver enlargement.

(7) The differential diagnosis at this point might include the following:

acute hepatitis (viral or alcohol-, chemical-, or drug-induced)
chronic active hepatitis (viral types B, C, D)
granulomatous or neoplastic infiltration

Among causes of acute hepatitis, alcohol is less likely because the SGPT level is greater than the SGOT level. With normal alkaline phosphatase, primary biliary cirrhosis or bile duct obstruction are also not probable.

(8) Viral hepatitis should be ruled out by serologic testing. Imaging studies such as CAT, MRI, or liver-spleen scan would be appropriate. An angiogram would be helpful if angiosarcoma is suspected. Direct indicators, such as urinary thiodiglycolic acid or vinyl chloride levels, would be helpful only if exposure to vinyl chloride were recent. Negative results in tests measuring these direct indicators, however, would not rule out drinking water contamination, for example.

(9) The differential diagnosis now most likely includes cirrhosis and malignancy. Hepatic angiosarcoma is not normally prominent in the differential diagnosis of liver function abnormalities. However, the test results thus far and the fact that this is a nonoccupational exposure to vinyl chloride (nonmalignant liver injury has not been reported in environmental exposures) make angiosarcoma of the liver a possibility. In the case of angiosarcoma of the liver, hepatic arteriography would reveal a characteristic appearance, with displacement of hepatic arteries, and a blush and "puddling" during the middle of the arterial phase. Percutaneous liver biopsy is contraindicated in cases of angiosarcoma because of the vascular nature of the tumor and the possibility of complicating thrombocytopenia or significant bleeding; laparoscopic biopsy would be more appropriate.

(10) Hepatic angiosarcoma grows rapidly and carries a poor prognosis. If untreated, most patients die within 6 to 12 months after diagnosis. The only long-term survivors have had the tumor successfully resected. As a precaution you might suggest that the patient ventilate new cars before entering them for prolonged periods and drive with the window open to maintain ventilation. Until the drinking water at his home is tested, the family should use bottled water to avoid any possible exposure there.

(11) Since the rest of the family and the nearby community may have had similar exposure to vinyl chloride, all should undergo periodic testing of transaminases, alkaline phosphatase, and serum bile acids to detect latent chemical injury. If these tests or an ICG clearance rate are positive for hepatic injury, biopsy may also be helpful. If the drinking water is not contaminated and there is no vinyl chloride waste disposal source to contaminate the water in the future, the exposure to the family and community has likely terminated.

(12) Your local, county, or state health department should be contacted and notified of the possible case. Because hepatic angiosarcoma is an extremely rare disease, even one case would alert public health authorities to a potential risk to the community around this plant. Your report should initiate case-finding investigations among the former workers at the plant as well as in the community. Public health authorities may also want to evaluate the potential for groundwater contamination around the plant.

Sources of Information

More information on the adverse effects of vinyl chloride and the treatment and management of vinyl chloride-exposed persons can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Vinyl Chloride Toxicity* is one of a series. For other publications in this series, please use the order form on the back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of Director, at (404) 639-0730.

Work-Related Disorders of the Neck and Upper Extremity

Lawrence J. Fine and Barbara A. Silverstein

A 31-year-old, right-handed man had been employed in a variety of automobile manufacturing jobs for 13 years. Two years ago he switched to a new plant and was assigned to a job that required him to move a spot welding machine beneath cars moving overhead. He had a minute to complete four welds on each car. The spot welder, which had metal handles, required substantial force for appropriate positioning, and it had to be repositioned four times for each car. The worker's wrists were in complete extension for a substantial portion of the job cycle.

When the worker started on this job, the weekday work shift was 9 hours long and Saturday work was required in most weeks. After 3 weeks on the job, he noted that he had pain in both wrists. He also noted numbness and tingling in the first four fingers on his left hand, first only at night, a few nights each week, after he had fallen asleep. When he awoke at night with the numbness, he would got up and walk around shaking his hands; in about ten minutes he would be able to go back to sleep. Gradually, over the next several months, the numbness and pain worsened both in frequency and intensity. His left hand would feel numb by the end of the work shift, and any time he was driving, his hands would become numb. Since he liked his job and did not want to be placed on restriction, which would mean he could not work overtime, he decided to visit his private physician rather than the company physician. He also was not sure that the company physician would be very sympathetic to his complaints.

His physician found on physical examination that he had decreased sensitivity to light touch in the left index and middle fingers and a positive Phalen's test of the left hand. She suspected carpal tunnel syndrome (CTS) and believed that the disorder might be work-related because the patient was young, male, and had no other risk factors, such as diabetes, past history of wrist fracture, or recent trauma to the wrist. The physician discussed job changes with the patient. She also prescribed wrist splints to be used only at night.

The splints relieved some of the nighttime numbness for a period. However, over the next 6 months, the patient's symptoms began to be present all of the time, and he thought that his left hand was becoming weaker. Similar symptoms also developed in his right hand.

The patient felt he could no longer do his job and returned to his physician. She noted that the Phalen's test was now positive bilaterally. She referred him to a hand surgeon and ordered nerve conduction tests because she was concerned that some surgeons do not always have these tests done before surgery. The nerve conduction test showed slowing of sensory nerve impulse conduction in the median nerve in the region

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of the carpal tunnel.

One year after the problem was first noted, he had surgery, first on the left hand and then on the right hand. Following surgery, the company placed him in a transitional work center for a 3-month period where he worked at his own pace and had no symptoms. He then returned to the assembly line with the restriction that he not use welding guns or air-powered hand tools. When he worked on the line, he occasionally had symptoms, but they were substantially less intense and less frequent than before.

He later transferred to a warehouse, because he felt that he would have a better chance of avoiding long layoffs there. He was placed on a job that required use of a stapling gun to seal packages. Three weeks after being placed in this job, his symptoms began to return with their former intensity. Through ordinary channels he immediately sought and was given a transfer to a position driving a fork lift truck. This change reduced, but did not eliminate, his symptoms. Currently he has numbness, tingling, and pain in the singers of both hands about twice a month. Playing volleyball usually triggers a severe attack. With the use of nighttime splints, he can sleep through most nights without awakening. While he feels that his hands are weaker than before he developed his symptoms, he is still able to perform his job. He has decided that as long as his symptoms remain at this level, he will continue working.

This case illustrates the intermittent and progressive nature of most work-related disorders of the upper extremity, and particularly of CTS, the best known of the common work-related disorders of the upper extremity. Other examples of these disorders that may be related to work include Quervain's disease, epicondylitis, rotator (or rotor) cuff tendinitis (mainly supraspinatus), and tension neck syndrome. This family of disorders may involve muscles (tension neck syndrome), tendons (supraspinatus tendinitis disease), joints (degenerative joint disease), skin (calluses), nerves (CTS), or blood vessels (hand-arm vibration syndrome, or Raynaud's phenomenon of occupational origin).

Contact Dermatitis in Surgeons from Methylmethacrylate Bone Cement

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In 1956, Fisher identified methylmethacrylate monomer as the cause of allergic dermatitis in four dentists and dental laboratory technicians who had come in repeated contact with acrylic denture materials, and this was also reported in one orthopaedic surgeon handling bone cement [2]. Methylmethacrylate monomer does diffuse through intact surgical rubber gloves [2]. An allergic eruption on the hands of one of the authors (I. B. F.) stimulated us to investigate the allergenic effects of bone cement.

Case Report

In 1972, I. B. F. frequently participated as assistant surgeon in cases of total joint replacements. Often this required that he mix and handle methylmethacrylate cement. Routinely the operation was done with two pairs of gloves, the outer pair being changed frequently. Often it was changed just prior to handling the cement.

A mild pruritis in the fingers first developed the night following operations, but no treatment was sought. Some paresthesias also developed which were attributed to over-tight gloves. However, larger gloves did not alleviate the symptoms.

At the end of 1972, he performed two joint-replacement procedures. Following the first he experienced pruritis, swelling, and erythema of the right and left index fingers and the right long finger. This subsided spontaneously in a few days. After the second operation, a week later, the same symptoms reappeared, this time associated with a localized vesicular eruption. Overnight incapacitating deep tenderness developed in these fingers, making it impossible for him to operate for three weeks.

Extensive patch tests were performed with a number of suspected contactants, but the only positive patch test was to methylmethacrylate monomer.

The dermatitis was successfully treated with topical steroid ointment. The skin of the affected fingers remained atrophic and scaling for about three weeks, and deep tenderness and parethesias lasted for about two months. After this episode, recurrence of the dermatitis was prevented by avoiding contact with bone cement, that is, the cement was handled by other members of the surgical team.

We collected thirteen cases of dermatitis in handlers of bone cement, including nine in active orthopaedic surgeons. Of these, seven demonstrated patch-test sensitivity to methylmethacrylate monomer (10 per cent in olive oil). We consider these seven to be cases of true allergic contact dermatitis characterized by itching, erythema, edema, and vesiculation followed by eczematization (Fig. 1). Three of

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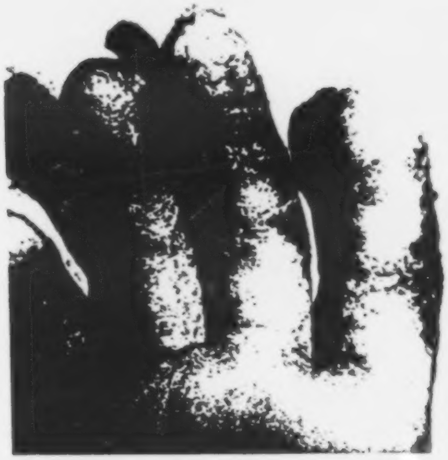

FIG. 1

the subjects showed complete resolution of their eruption with careful avoidance of the monomer, but did not demonstrate a positive patch test. We do not consider their reactions to be allergic. The dermatitis was marked by the presence of dryness and fissuring of the finger tips, but without pruritis and vesicle formation. Three of the patients were identified through correspondence and have not yet been fully characterized as allergic.

The observations of Pegum and Medhurst led us to examine different types of surgical gloves in the hope of finding one that would successfully isolate the surgeon's hands from the monomer. Glove fingers were cut off intact gloves and filled with small amounts of powdered polymer. The tips of these filled glove fingers were immersed in glass vials containing monomer. A test period of twenty minutes was chosen as the maximum time a surgeon might be in contact with the bone cement during any one operative procedure. After twenty minutes the filled glove fingers were removed from the monomer and the contents were examined. In all cases partial to complete polymerization of the powdered polymethylmethacrylate was noted, indicating that monomer had diffused directly through the gloves.

The majority of the gloves also showed evidence of direct attack by the monomer. One type of glove completely disintegrated. The vinyl glove tips were markedly affected, and most latex rubber gloves showed wrinkling and brittleness. In many of the trials the monomer solution was discolored by leaching of dye from the gloves. In approximately one-third of the samples the polymerized cement also took on coloration from contact with the gloves (Table I).

The unique and consistent feature of the dermatitis from bone cement was paresthesia. Deep tenderness was also common and outlasted the duration of the eruption.

Methylmethacrylate monomer is a lipid solvent. The irritant effect of the monomer is probably due to its ability to degrease the skin and penetrate the subcutaneous tissue. Apparently some surgeons with a mild sensitivity are able to avoid the dermatitis by using three layers of gloves during handling of the cement, and then immediately removing the outer two, or possibly all three gloves. Multiple gloves tend

TABLE I

GLOVE TESTS

Type of Glove	Polymerization after 20 Min.	Glove Damage	Monomer Discolored	Polymer Discolored
Abbott — Latex Surgeon's	+ + +	+ +	+	−
Arbrook Micro-touch, Latex Medical	+ +	+	−	−
Arbrook Micro-touch, Vinyl Medical	+ + +	+ +	−	+
Arlin Poly-Version (Polyethylene)	+	+	−	−
Bard Parker, Thru-touch Vinyl	+ + +	+ +	+ +	+
Ducpren Elastren	*	+ + + +	+	*
Dart Industries "Seamless" Limber Latex Surgeon's	+ +	+	−	−
Dart Industries "Seamless" Original Brown Milled Surgeon's	+ + +	+ +	+ + +	+ + +
Dow Silastic Sheet	+ + +	+ +	−	−
Fisher Polygloves (Polyethylene)	+	−	−	−
Parke Davis Eudermic Surgeon's	+ + +	−	−	−
Parke Davis Examination	+ + +	+ + +	−	+ +
Parke Davis "Spectra" Surgeon's	+ + +	+	+	−
Perry Latex Surgeon's	+ + +	+	+	+
Perry Latex Surgeon's Orthopaedic	+ +	+	+	−
Pioneer	+ +	+	−	−
Tomac Latex Exam	+ + +	−	+	+
Tomac "Thin-tip"	+ + +	+	+	−

* No polymerization, glove disintegrated.

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to retard and reduce diffusion, proportionally to the number of layers. However, diffusion is not prevented and the monomer tends to be kept in contact with the skin. Merely painting methylmethacrylate monomer on the skin of a sensitive subject has been shown not to cause an allergic reaction because the monomer evaporates so rapidly. However, if the monomer is applied under an occlusive or semi-occlusive dressing, a reaction will ensue in the sensitive subject.

Synthetic gloves are currently under development that we hope will be impervious to methylmethacrylate monomer.

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ATSDR
May 1993

Case Studies in Environmental Medicine

28

Skin Lesions and Environmental Exposures
Rash Decisions

Environmental ALERT . . .

- ☑ ***Dermatitis accounts for about 30% of all illnesses in the workplace; the prevalence of skin diseases caused by chemicals in the environment is unknown.***
- ☑ ***A thorough exposure history is the most important element in accurate diagnosis of skin lesions.***
- ☑ ***In some cases, skin lesions are a diagnostic clue to the presence of systemic toxicity.***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. See page 45 for more information about continuing medical education credits and continuing education units.

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Introduction

Unlike most organs, the skin is in constant contact with the external environment. The skin ensures the body's integrity by preserving internal fluids and electrolytes, maintaining thermoregulation, and protecting against physical injury and entry of harmful agents. Because the skin has such a prominent and protective role, many factors affect it adversely, including mechanical agents (friction, vibration, pressure, and trauma); physical agents (heat, cold, and radiation); biologic agents (plants, insects, animals, and microbes); and a variety of chemical agents.

The large number of chemicals in the home and workplace and the accidental and intentional releases to air, water, and soil potentially allow ever-increasing contact with chemicals in the environment. Dermatitis from chemical exposures in the workplace accounts for about 30% of all reported occupational illness; the prevalence of skin lesions due to chemicals encountered outside the workplace (i.e., environmental exposures) may never be known.

Seven common skin conditions that can have environmental etiologies are presented in this monograph. Accurate diagnoses and identification of etiologies are necessary, not only to properly treat skin diseases, but also to prevent future occurrence of disease or exposure.

Familiarity with the vocabulary of dermatology is helpful in understanding this specialized topic. A glossary of terms begins on page 42.

Pretest

(a) *What are the most likely nonoccupational etiologies for four of the more common skin conditions: irritant and allergic contact dermatitis, urticaria, and photosensitivity?*

(b) *What are the most effective treatments and preventive measures for each of these skin conditions?*

Answers begin on page 39.

Case 1 — Irritant Contact Dermatitis

A husband and wife consult you because of skin rashes that have developed since they began renovating a recently purchased older home. They have no history of skin problems.

The man complains of severe itching of the hands and an erythematous rash with papules and excoriations on the arms and lower legs. This rash began during the time he was placing new insulation in the attic.

The woman complains of a rash with redness and a small amount of blistering on the hands and wrists. There is mild itching, and some painful fissures have formed on the fingertips. The rash developed over a period of several days, beginning with only erythema while she was using a commercial paint-stripping product to remove old paint from interior trim. Although she wore rubber gloves, some of the stripping compound came in contact with her skin by running down into the gloves from the wrist area and through small holes in the fingers.

Challenge

(1a) What is the most likely cause of the husband's rash? How could this be confirmed?

(1b) What are the most likely causes of the woman's rash?

(1c) How would you treat the skin lesions experienced by these patients?

Description

☐ **More than 90% of skin lesions caused in the workplace are contact dermatitis.**

☐ **Lesions of irritant contact dermatitis are localized and the symptoms are generally less severe than those of allergic contact dermatitis.**

In the occupational exposure setting, the most common skin lesions (greater than 90%) are dermatitis due to either contact irritation or contact allergy, with irritant contact dermatitis being reported more frequently.

Irritant contact dermatitis caused by chronic exposure to mild irritants typically begins with erythema and progresses to eczema with exudative vesicles and papules, most often limited to the area of direct contact. Itching, stinging, and burning sensations may be noted—especially with stronger irritants—but are generally not as severe as symptoms of patients who have allergic contact dermatitis. (For a discussion of allergic contact dermatitis, see page 9.)

After days to weeks of chronic irritant exposure, the skin may become lichenified. Painful fissures may develop, along with hyperpigmentation, crusts, and scales. When contact with the offending irritant is discontinued, the rash usually resolves spontaneously in 1 to 3 weeks. Irritant contact dermatitis rarely spreads to areas of the body remote from the site(s) of direct contact.

Cutaneous hardening can develop when patients with irritant contact dermatitis have daily exposure to irritating substances. The skin becomes tough and resistant at the sites of contact, allowing further exposure to the irritant but without reaction. If exposure ceases, however, this protective adaptation is lost rapidly.

Pathophysiology

☐ **Irritant contact dermatitis is caused by direct action of irritants on the skin.**

Irritant substances cause dermatitis by direct chemical action (i.e., nonimmune-mediated) on contacted components of the skin. Irritants may be acidic substances, which coagulate skin proteins, or alkaline substances, which remove surface lipids. Both types of substances may cause drying and cracking of the skin. Epidermal necrosis with separation of the epidermis from the underlying dermis results in formation of vesicles that contain mainly polymorphonuclear (PMN) leukocytes. Vesicles and bullae with both PMN leukocytes and lymphocytes occur in the upper portion of the dermis.

Common Etiologies

Almost any substance can be a contact irritant (Table 1), although some substances, such as some alcohols, oils, and glycols cause irritant contact dermatitis in only a small percentage of exposed persons. In contrast, strong irritants, such as concentrated mineral acids, alkalies, and amines, cause chemical burns or irritant contact dermatitis in almost everyone exposed. Mild to moderate irritants (e.g., dilute acids, organic hydrocarbon solvents, and some detergents) generally produce irritant dermatitis in only a small percentage of persons after a single contact but will cause a reaction in nearly everyone after prolonged or repeated exposure.

Table 1. Common irritants in the home and workplace*

Home

- Bleaches
- Copper and metal brighteners
- Detergents
- Drain cleaners
- Fertilizers
- Furniture polishes and waxes
- Oven cleaners
- Pesticides
- Pet shampoos
- Rug shampoos
- Scouring pads and powders
- Soaps
- Toilet bowl cleaners
- Window cleaners

Workplace

- Acids and alkalies
- Cleaning products
- Epoxy resins
- Foams (e.g., insulation foams)
- Noncarbon-required (NCR) paper
- Powders
  - Aluminum
  - Calcium silicate
  - Cement
  - Cleaning agents
  - Metallic oxides
- Particles
  - Ore particles in mining
  - Plant particles
  - Plastics, dry
  - Sawdust
  - Wool
- Volatile substances
  - Ammonia
  - Formaldehyde
  - Organic solvents

*Adapted from Robert M. Adams, Occupational skin disease, 2nd edition. Philadelphia: W.B. Saunders Co., 1990.

The young are generally more susceptible to irritant contact dermatitis than adults are because the threshold for skin irritation is low in children, particularly infants. Irritation reactivity gradually lessens after about 8 years of age. During play, children are likely to have skin contact with soils containing hazardous substances or with wooden playground structures that may have been treated with irritating chemicals such as arsenate and pentachlorophenol. The occurrence of skin problems is also common in the elderly. Besides age, personal factors that predispose persons to irritant contact dermatitis include genetic constitution and previous episodes of eczema.

Environmental and physical factors influence the skin's susceptibility to irritant contact dermatitis. Susceptibility is often enhanced by wet work and conditions such as cold and windy weather, low relative humidity, and high temperatures that cause sweating. Some anatomic regions are more sensitive than others. Friction and lacerations or other mechanical skin injury may facilitate the development of irritant contact dermatitis. Occlusion by protective equipment such as gloves provides a humid environment, minimizing evaporation and making the stratum corneum more permeable to chemical substances that come in contact with the skin.

Diagnosis

☐ **Onset of irritant contact dermatitis tends to be insidious.**

Irritant contact dermatitis is often difficult to differentiate from allergic contact dermatitis. Routine skin biopsy generally is not helpful because the histologic appearance of irritant and allergic contact dermatitis is similar. However, unlike allergic contact dermatitis, irritant contact dermatitis tends to localize at the exposed area and to cause mild itching and more erythema than vesiculation. The onset of irritant contact dermatitis is insidious rather than explosive. Patch testing by, or in consultation with, a dermatologist may be necessary to reach a diagnosis or to exclude allergic contact dermatitis. If fibrous glass is the suspected irritant, skin scrapings suspended in a few drops of 10% potassium hydroxide and examined under a light microscope at low power may reveal glass fibers.

Treatment

☐ **Removal from exposure is the most important step in treating irritant contact dermatitis.**

The most important step in treatment is to remove the patient, at least temporarily, from further exposure to the offending agent. Substituting less irritating chemicals for the offending substance and correctly using protective materials, such as gloves and barrier creams, may help reduce exposure. During healing, the skin should be protected from other insults such as frequent washing, trauma, wind, and rapid changes in temperature.

Treatment for acute vesicular irritant contact dermatitis includes topical application of wet dressings for 15 to 20 minutes, 3 to 6 times daily. Domeboro's solution (diluted 1:40) or Burow's solution may be used to soak the dressings. Dressings should be discontinued after 2 to 3 days to avoid drying the skin.

☐ **Topical corticosteroids may be useful in cases of irritant contact dermatitis.**

Topical application of corticosteroid preparations may be efficacious. A low-potency corticosteroid should be used for mild to moderate skin conditions, with progression to more potent corticosteroids as required (Table 2). Some over-the-counter and prescription topical medications or their excipients can further irritate the skin or provoke allergic contact dermatitis. Administering mild sedatives and antihistamines to relieve itching may also be beneficial.

Clinical signs of secondary bacterial infection include increased erythema and tenderness; development of a yellow, crusting, or purulent exudate; and occasionally, formation of small pustules around the edges of the dermatitis. Infection with monilia has an appearance similar to bacterial infection, except that the exudate is usually white. Infection may be difficult to recognize initially because the serous exudate and erythema of the dermatitis can obscure the signs. Obtaining samples of the exudate for culture and sensitivity before initiating topical or systemic antibiotic therapy is generally advisable.

Table 2. Groups of topical corticosteroid products, in order of decreasing potency*

Drug	Trade Name†	% Concentration
Group 1		
Betamethasone dipropionate	Diprolene	0.05
Halbertasol propionate	Ultravate	0.05
Clobetasol propionate	Temovate	0.05
Diflorasone diacetate	Psorcon	0.05
Group II		
Amcinonide	Cyclocort	0.1
Betamethasone dipropionate	Diprosone	0.05
Desoximetasone	Topicort	0.25
Diflorasone diacetate	Florone, Maxiflor	0.05
Fluocinolone acetonide	Synalar–HP	0.2
Fluocinonide	Lidex	0.05
Halcinonide	Halog	0.1
Triamcinolone acetonide	Aristocort, Kenalog, etc.	0.5
Group III		
Betamethasone benzoate	Benisone, Uticort	0.025
Betamethasone valerate	Betatrex, Beta-Val	0.1
Desoximetasone	Topicort LP	0.05
Flurandrenolide	Cordran	0.025
Hydrocortisone valerate	Westcort	0.2
Triamcinolone acetonide	Aristocort, Kenalog, etc.	0.1
Group IV		
Betamethasone valerate	Valisone, Reduced Strength	0.01
Clocortolone pivalate	Cloderm	0.1
Fluocinolone acetonide	Fluonid, Flurosyn, Synalar, etc.	0.025
Flurandrenolide	Cordran SP	0.025
Triamcinolone acetonide	Aristocort, Kenalog, Triacet	0.025
Group V		
Alclometasone dipropionate	Aclovate	0.05
Desonide	DesOwen, Tridesilon	0.05
Fluocinolone acetonide	Fluonid, Synalar	0.01
Group VI		
Dexamethasone	Aeroseb-Dex, Decaderm	0.01-0.1
Hydrocortisone	(generic, over-the-counter)	0.25-2.5
Methylprednisolone acetate	Medrol	0.25-1.0

Adapted from RC Cornell and RB Stoughton. The use of topical steroids in psoriasis. Dermatol Clin 1984;2:397-409.

* No significant difference exists among agents in a group. These products come in various forms (i.e., creams, gels, lotions, solutions, and ointments), although some products are not available in all forms.

† Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

Case 2 — Allergic Contact Dermatitis

You are consulted by a 44-year-old male office worker who has a chief complaint of a rash on his hands and wrists. His company recently relocated from a building where each employee had a private office to an older, renovated building with large bay areas. New wallboard was placed, the area was painted, and new carpet was laid just before the move. Employees now work in cubicles; the patient's cubicle is located in an interior area with no windows. A copying machine is adjacent to his work area.

Since the move, many of the patient's coworkers have been complaining of unpleasant odors, a feeling of fatigue or excessive tiredness, and mild irritation of the eyes, nose, and throat. They associate these symptoms with working in the new area. Although the patient has not noted such symptoms, he does complain of the increased noise and distraction in the new work area; he feels that his rash is somehow related to the new location.

The rash began 5 days ago with itching and redness. It then developed weeping and raised, vesicular lesions that spread from the initial location on the hands to the volar surfaces of the wrists. The patient states that he has a history of reaction to poison ivy, which produces a similar rash, but he has not been in an infested area for the past 2 months. He has no direct contact with industrial cleaning agents or carbonless copy paper in his work. He does have contact with chemicals through his woodworking hobby. He recently built an end table from exotic Japanese woods and has been applying a varnish that a friend brought from Japan.

Challenge

(2a) Could the patient's rash be due to airborne allergens or irritants in the new office location?

(2b) Could the rash be related to his woodworking hobby?

(2c) What is the most effective treatment for this patient?

Description

- ☐ **About 30% of occupational skin disorders are allergic contact dermatitis.**
- ☐ **In sensitized persons, inflammation begins about 12 hours after exposure to an allergen.**

Although contact allergens produce sensitization in only a small percentage of exposed persons, allergic contact dermatitis constitutes about 30% of the skin disorders found in the workplace. Once a person has been sensitized to an offending substance, further exposure may result in relatively rapid development of local inflammation with erythema, papule formation, induration, and weeping vesiculation. Inflammation usually begins about 12 hours after exposure; intensity peaks in 50 hours or more. The rash may spread locally around the margins of the original site or to distant sites that did not have contact with the allergen. Potentially, the entire skin surface could become involved (a condition known as erythroderma or exfoliative dermatitis).

Pathophysiology

- ☐ **Cross-reactivity with antigenically similar substances can occur with allergic contact dermatitis.**
- ☐ **The clinical and histologic appearances of allergic and irritant contact dermatitis are similar.**

Allergic contact dermatitis results from a true allergic (i.e., cell-mediated) sensitization to the offending substance. Cross-reactivity with antigenically similar substances may occur. Initially, during the refractory period, the patient may be exposed without developing a reaction. During the induction phase, which may last from 4 days to several weeks (usually about 14 to 21 days), the development of complete allergic sensitization occurs as the allergen comes in contact with the skin. After the skin is fully sensitized, further contact with the allergen may result in rapid and severe dermal manifestations. When no further contact with the allergen occurs, the patient is in the period of persistence of sensitivity. The level of sensitivity can decrease over time, but sensitization may be lifelong.

Most allergens that cause allergic contact dermatitis have molecular weights of less than 500 daltons. The allergens are haptens rather than complete antigens; they must penetrate the skin and combine with endogenous proteins to form full antigens. Langerhans cells play a key role in then presenting the antigen to T lymphocytes, thereby activating the T cells. The sensitized T cells proliferate in the paracortical regions of the lymph nodes and produce effector and memory lymphocytes that remain in the general circulation. On subsequent contact with the complete antigen, the effector cells release lymphokines that may result in rapid and severe, local inflammation.

Many factors can affect the development of allergic contact dermatitis, including characteristics of the allergen itself, patient factors, and environmental conditions. Allergen factors include the physiochemical nature of the allergen (e.g., lipophilicity, solubility, and inherent sensitizing potency), concentration, total dose that comes in contact with the skin, anatomic site of contact, number and frequency of exposures, and occlusion by clothing or gloves.

The most important predisposing patient factors are a history of irritant contact dermatitis and the presence of an inflammatory skin condition that may promote absorption of the allergen. Irritant dermatitis caused by household cleaning agents on women's hands may continue as allergic nickel dermatitis (from costume jewelry). In addition, age and genetic predisposition can influence the development of allergic contact dermatitis. Persons who have histories of atopic dermatitis have been reported to have *decreased* risk of developing allergic dermatitis but *increased* risk of developing irritant dermatitis.

Common predisposing environmental factors for allergic contact dermatitis are pressure, friction, heat, and prolonged immersion in water (such as occurs during wet work). Relative humidity, ambient temperature, and season of the year also play roles in development of allergic contact dermatitis.

Common Etiologies

☐ **Aromatic compounds with polar or ionic substituents are potent sensitizing agents.**

Only several hundred of the thousands of chemicals used are known to cause allergic contact dermatitis. With the exception of nickel, cobalt, and some forms of chromium, most metals do not produce sensitization. Strong inorganic alkalies and acids seldom cause allergic reactions. Although a substance's sensitization potential cannot be determined from its chemical structure alone, some chemical classes are more likely to cause allergic contact dermatitis (see Table 3). Aromatic compounds with polar or ionic substituents are typically sensitizing agents (e.g., *p*-aminophenol and hydroquinone used in photographic film developers).

In addition, chemicals that are structurally similar to the original sensitizing agent may provoke recall of the specifically sensitized lymphocytes, a phenomenon known as cross-sensitization. For example, persons exposed to p-phenylenediamines used in the rubber industry may react to related substances used in photographic developers and dyes. Persons sensitized to *Rhus* plants such as poison ivy or poison oak may be sensitive to cross-reacting substances found in exotic trees and their derivative products (lacquers, varnishes, and oils).

Table 3. Some chemical groups known to cause allergic contact dermatitis

Aromatic amines
Benzothiazoles
Caine-type anesthetics
Ethylenediamine compounds
Halogenated germicides
Hydroxyquinolines
Phenolic compounds
Phenothiazines
Streptomycin group of antibiotics
Thiurams

Synthetic substances that commonly cause allergic contact dermatitis are rubber products, plastic resins, organic dyes, topical medications, germicidal and biocidal preparations, and various commercial and medication ingredients (Table 4). Natural products can also produce allergic contact dermatitis. Exposure to certain airborne contaminants may also cause allergic contact dermatitis. Airborne contaminants include dichromates in cement dust, rosins used in soldering operations, and sawdust.

Table 4. Common causes of allergic contact dermatitis

Germicides and biocides
- Formaldehyde-releasing compounds
- Parabens
- Quaternary ammonium compounds

Grains
- Barley
- Oat
- Rye
- Wheat

Foods/Spices
- Cardamon
- Carrot
- Chicory
- Coconut
- Coffee
- Endive
- Lettuce
- Potato
- Radish
- Tamarind
- Tumeric
- Vanilla

Medication/product ingredients
- Preservatives
  - Lanolin
  - Thimerosal
- Fragrances and perfumes
  - Balsam of Peru
  - Benzyl alcohol
  - Cinnamic acid derivatives
  - Citronella derivatives

Metals
- Chromium
- Cobalt
- Nickel

Organic dyes
- *p*-Aminoazobenzene
- *p*-Phenylenediamine

Plastic resins
- Epoxies
- Formaldehyde-based acrylics
- Phenolics

Rhus* plants
- Poison ivy
- Poison oak
- Poison sumac

Rubber products
- Antioxidants
- Polymerization accelerators

Topical medications
- Benzocaine
- Neomycin

* For a more complete listing of plants that cause dermatitis see R.M. Adams, Occupational skin disease, 2nd edition, Philadelphia: W.B. Saunders Co., 1990, p. 507-9.

Diagnosis

☐ **Allergic contact dermatitis often spreads to areas remote from the site of contact.**

Allergic contact dermatitis is often misdiagnosed as irritant contact dermatitis. Other conditions to consider in the differential diagnosis are atopic dermatitis, pustular eruptions on the palms and soles, psoriasis, *Herpes simplex* and *Herpes zoster*, insect bites, parasite infestation such as scabies, fungal infections of the feet with idiopathic vesicular reactions, nummular eczema, drug eruptions, and erythema multiforme.

Skin Lesions

No distinctive features of the lesions facilitate the differentiation of allergic from irritant contact dermatitis. An important diagnostic clue to allergic contact dermatitis is the spread of rash to areas remote from the site of contact; the mucous membranes are usually spared, and the scalp, soles, and palms are often unaffected.

Patch testing (see *Diagnostic Procedures*, page 35) may help differentiate allergic from irritant contact dermatitis. Because the histologic appearance of lesions due to allergic or irritant contact dermatitis is the same, routine skin biopsy is not helpful in their differentiation.

☐ **The clinical and microscopic appearances of skin lesions due to allergic contact dermatitis are the same as those due to irritant contact dermatitis.**

Treatment

At present, there are no satisfactory means of desensitizing humans to allergens. The most important step is to remove the patient from exposure to the offending substance. In the workplace, options such as protective clothing and substitute chemicals should be explored. The therapy for allergic contact dermatitis is the same as that for irritant contact dermatitis (see *Treatment, Irritant Contact Dermatitis*, page 6).

Systemic corticosteroids may be indicated for some patients who have allergic contact dermatitis, especially when large areas of the skin (20% total body surface area or greater) are involved. Short courses of oral corticosteroids, particularly if used for a *Rhus*-induced contact dermatitis, may be given for 2 to 3 weeks (up to 21 days). Corticosteroids administered even for a short period of time should always be delivered in decreasing doses over the course of therapy to prevent adrenal suppression.

☐ **Treatment for allergic contact dermatitis is identical to that for irritant contact dermatitis.**

Case 3 — Photosensitivity Contact Dermatitis

You are consulted by the headmaster of a children's summer camp because of an outbreak of skin rashes in 20 of the campers. No counselors are affected. On examination, the rashes, which are confined to the hands, wrists, and forearms, consist of discrete linear streaks and patches that are hyperpigmented and do not itch.

One of the staff members speculates that the rashes are caused by contact with an epoxy glue used in building a model. However, only two of the children who have rashes have been involved in this activity. All the affected children had participated in a craft class in which they made lime sachets by puncturing lime skins and inserting sprigs of cloves over the surfaces of the limes. During the class, they also prepared gift cards from recycled paper. While the children attended to these activities, the counselors were engaged in planning an outdoor activity that was to follow the craft session.

Challenge

(3a) What causes of the children's dermatitis might be considered, given the rural location and nature of camp activities?

(3b) What treatment would you recommend?

Description

- ☐ **Photosensitivity reactions occur mainly on sun-exposed areas of the body.**
- ☐ **Photoallergic reactions are immune-mediated responses; phototoxic reactions are not.**

Photosensitivity contact dermatitis occurs mainly on sun-exposed areas such as the face, upper chest, posterior portion of the neck, extensor surfaces of the forearms, dorsum of the hands and feet, and anterior surfaces of the lower legs. Areas of the skin normally covered by jewelry and clothing are spared, as are eyelids, areas under the chin, and upper portions of the ears covered by hair. Photosensitivity contact dermatitis may be the result of phototoxicity or photoallergy.

Lesions of phototoxic and photoallergic contact dermatitis resemble those of irritant and allergic contact dermatitis. They have been described as discrete, confluent, polymorphous linear streaks and patches that are macular and nonpruritic. The patient may experience a stinging or burning sensation of the skin, typically beginning shortly after exposure to sunlight and resolving rapidly when the skin is shaded. Lichenification and hyperpigmentation may occur, and the lesions may persist for months or years. In some cases, widespread involvement of the skin develops later. The photoallergic response usually occurs in only a small number of persons who have been previously sensitized to the photoactive agent.

Pathophysiology

- ☐ **Sunlight can cause formation of the agents that result in photosensitivity contact dermatitis.**

The mechanisms of photosensitivity contact dermatitis are broadly analogous to the mechanisms of irritant and allergic contact dermatitis except for the added requirement of appropriate ultraviolet (UV) radiation (i.e., wavelengths of 315 to 400 nanometers, known as UV-A). The agent that provokes the irritant or allergic response is formed after its precursor has been exposed to UV-A.

In phototoxicity, the excited state of the agent produced during irradiation is thought to lead to oxidation of cellular components or to allow binding of the agent with nucleic acids. In photoallergy, the initial reaction of the topical agent with UV-A forms either an excited molecule that can bind with protein to form a complete allergen or a product that is itself a strong contact allergen.

Common Etiologies

- ☐ **Many topical products can produce photosensitivity dermatitis.**

Many products that cause photosensitivity dermatitis are applied topically. Common examples are lotions containing fragrances; suntanning products with ultraviolet absorbers such as 6-methylcoumarin, homosalicylate, or *p*-aminobenzoic acid (PABA); and aftershave lotions containing musk ambrette. Germicides in soaps and detergents may also cause photosensitivity dermatitis. A major epidemic of allergic contact dermatitis occurred in Great Britain in 1960 after the introduction of two soaps that contained tetrachlorosalicylanilide, a photoactive antibacterial agent.

Skin Lesions

Certain systemically administered medications have caused photoallergic drug reactions. Examples include nalidixic acid, phenothiazines, sulfonamides, sulfonylureas, tetracyclines, and thiazide diuretics. Pharmacists, nurses, and others who routinely have skin contact with these drugs are prone to photosensitivity dermatitis.

Plants such as celery and citrus fruits have caused phototoxic dermatitis in persons who handle them extensively; farm workers are particularly susceptible. Contact with oil released from lime skins or with coal tar and pitch has resulted in phototoxic dermatitis, especially in lightly pigmented persons.

Psoralens, which are photoactive and can cause phototoxic dermatitis, are also used therapeutically in the treatment of psoriasis. In PUVA (psoralen plus UV-A radiation) treatment, a psoralen is painted on the affected skin or given systemically to patients who are then exposed to UV radiation. The photoadduct that is formed between the psoralen and DNA serves to slow the rate of the psoriatic overgrowth.

- ☐ **Psoralens, which can cause phototoxic dermatitis, are useful in the treatment of psoriasis.**

Diagnosis

Photoallergy from chemical contact must be differentiated from polymorphous light eruption, systemic lupus erythematosus, pellagra, dermatomyositis, porphyria, allergic contact dermatitis and photoallergic drug reaction. A thorough history of medication treatment will usually rule out photoallergic drug reaction.

Photopatch testing may be useful in confirming the diagnosis, but results of photopatch testing are often difficult to interpret and are best left to dermatologists with specialized equipment and knowledge in this field.

- ☐ **A thorough drug history will usually rule out photoallergic drug reactions.**

Treatment

The treatment for phototoxic or photoallergic dermatitis is the same as the treatment for irritant and allergic contact dermatitis (see pages 6 and 13). Identifying the offending agent and counseling the patient to avoid further exposure to it are the most important interventions. When the photosensitizing agent cannot be avoided, limiting sunlight exposure and wearing protective clothing, such as hats, gloves, long-sleeved garments, socks, and shoes, may help. Sunscreens may be used if reaction or cross-sensitivity between the causative agent and components in the sunscreen is not a possibility.

- ☐ **Treatment for phototoxic and photoallergic dermatitis is the same as that for irritant and allergic contact dermatitis.**

Case 4 — Chloracne

A 42-year-old man consults you because of a persistent skin condition that he feels resembles the cosmetically displeasing acne he had as a teenager. His present skin condition consists of pale yellowish, cystic lesions and comedones localized on the face, below and lateral to the eyes, and behind the ears. Similar lesions are present on the cheeks, forehead, and neck; a few are present on the buttocks, where, according to the patient, he never had lesions with his prior affliction. He also complains of moderately severe itching.

History reveals no changes in diet, and the patient is not taking medications. For the last 15 years, the patient has worked for a local utility company. His most recent job duties have included replacing the heat exchange fluids in transformers. He first noted the rash about a month ago; he is not certain whether the rash appeared before or after he began this activity.

Challenge

(4a) Is the skin condition described by the patient consistent with a reactivation of acne vulgaris? What other causes should be considered?

(4b) What therapy would you recommend?

Description

- ☐ **Chloracne is rare and is usually due to occupational exposure to chloracnegenic agents.**
- ☐ **Chloracne may be an indication of systemic toxicity.**

Environmental acne is a variety of acne venenata typically caused by industrial chemicals. It may result from contact with petroleum and its derivatives (oil acne), coal tar products (coa-tar-pitch acne), and halogenated aromatic hydrocarbons (chloracne). Environmental acne may also be caused by certain physical, mechanical, and biologic agents. Although the occurrence of chloracne is rare (probably fewer than 4000 cases worldwide), it is of great concern because it is an extremely refractory acne and because it may be indicative of systemic toxicity by a highly toxic chemical.

The lesions of chloracne consist of straw-colored cysts, numerous comedones, milia, and papules. The lesions are located on the face (especially at "crow's feet" and below and to the outside of the eyes [malar crescent]), neck, earlobes, shoulders, abdomen, legs, buttocks, and genitalia. The nose is often spared. With severe chloracne, all the follicles in an area may be involved, resulting in a rather bizarre "pebbled" appearance. Pruritus is common and occurs in about 50% of chloracne cases.

Pathophysiology

- ☐ **Chloracne is often refractory to treatment.**

Onset of disease is typically delayed 2 to 4 weeks after exposure to a chloracnegenic agent. The first changes are a thickening of the follicular epithelium, development of comedones, and a slow disappearance of the sebaceous glands as they are replaced by keratinous cysts. Initially, inflammation is uncommon; inflammatory lesions with larger cysts and abscesses are later developments. Severe scarring may occur. Increased fragility of the skin, hypertrichosis, widespread follicular hyperkeratosis, or hyperpigmentation may develop. A brownish discoloration of the nails, swollen eyelids, and conjunctivitis or discharge may be present in some patients.

With no additional exposure, the disease will first progress, then regress over a 4- to 6-month period. A few cases of chloracne have persisted for 30 years or more after contact with the chloracnegenic agent has ceased.

Common Etiologies

- ☐ **Chlorinated aromatic hydrocarbons cause chloracne.**

Many chlorinated aromatic hydrocarbon compounds used in the workplace can cause chloracne. These compounds include chlorinated naphthalenes, polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), dioxins, polychlorinated dibenzofurans, pentachlorophenol, azobenzenes, and azoxybenzenes. (See *Case Studies in Environmental Medicine: Polychlorinated Biphenyl (PCB) Toxicity, Case Studies in Environmental Medicine: Dioxin Toxicity, and Case Studiies in Environmental Medicine: Pentachlorophenol Toxicity.)*

Diagnosis

Chloracne must be differentiated from oil acne or folliculitis due to exposure to grease and oils; acne vulgaris; acne cosmetica from heavy cosmetic use; acne mechanica from local pressure and friction; acne medicamentosa from medications such as corticosteroids, hormonal preparations, phenytoin, iodides (e.g., in kelp tablets), bromides and solar elastosis with comedones.

A history of exposure to agents known to cause chloracne and the typical appearance of the rash on physical examination are usually sufficient for diagnosis. Chloracne may be distinguished from acne vulgaris by the distribution of the lesions, age at onset, and morphology. Chloracne lesions typically affect the face, neck, earlobes, shoulders, abdomen, legs, buttocks, and genitalia, whereas lesions of acne vulgaris are found primarily on the face, neck, chest, and back (down to the waist). Chloracne can appear at any age, whereas acne vulgaris is seen most often in patients aged 13 to 26 years. Chloracne lesions consist of straw-colored cysts, numerous comedones, milia, and papules; whereas the lesions of acne vulgaris are typically comedones, papules, pustules, and scars.

Histologic examination of cysts may show typical changes, but the usefulness of biopsy in establishing the diagnosis is questionable. Associated noncutaneous conditions found in some patients who have chloracne include hepatotoxicity, porphyria cutanea tarda, and peripheral neuropathies.

- ☐ **Chloracne must be differentiated from other more common acnes.**

Treatment

Primary interventions are prevention of exposure to chloracnegenic chemicals and good hygiene because a satisfactory treatment regimen cannot be found in many cases. Administration of oral antibiotics and acne surgery have been of limited success. Retinoic acid (vitamin A) preparations or 13-cis-isoretinoic acid (Accutane) have been successful in carefully selected patients. (Note: Accutane is a known teratogen and should be used cautiously.) Injecting inflamed lesions with dilute triamcinolone, a glucocorticoid, may be helpful, as may dermabrasion for severe scarring.

- ☐ **Removal from exposure to chloracnegenic agents is the most important treatment for chloracne.**

Case 5 — Pigment Alterations

Fifteen children from a local school are referred by the school nurse for evaluation of skin lesions. The lesions consist of decreased pigmentation in a scattered distribution. Two of the children have histories of itchy, weeping, vesicular rash on the neck and face that cleared before the pigment changes became noticeable. A public health evaluation of the drinking water and food served at the school has not revealed toxic or infectious agents. The school is located near a chemical manufacturing facility, in which the parents of several children work, including the parents of the two children who have histories of vesicular rash.

Challenge

(5a) *Could the nearby manufacturing facility be associated with the decreased pigmentation noted in the children in this case?*

(5b) *How could you investigate this possibility?*

(5c) *What treatment options are available for persistent hypopigmentation involving large areas of the skin?*

Description

☐ **Pigment changes are usually associated with post-inflammatory effects from physical or chemical agents.**

A variety of physical and chemical agents may affect the color of the skin. Insults to the skin may cause either increased pigmentation (hyperpigmentation), decreased pigmentation (hypopigmentation), or both in contiguous areas (dyschromia). Inflammation, which may be subclinical and not apparent, usually precedes pigment alterations. Postinflammatory reaction (e.g., to contact dermatitis) is the most common cause of increased pigmentation, although pigment loss may also occur.

Pathophysiology

☐ **Hypopigmentation is caused by damage to the melanocyte or through inhibition of melanin synthesis.**

☐ **Hyperpigmentation is often caused by nonspecific skin damage that leads to melanin or hemosiderin accumulation.**

In hypopigmentation, depigmentation probably occurs either by damage to the melanocyte, which leads to cell distortion and death, or through inhibition of melanin synthesis by the offending substance. It may be significant that industrial compounds that cause hypopigmentation (Table 5) are structurally similar to tyrosine, the building block of melanin. In industrially related hypopigmentation (leukoderma), the hands, wrists, and forearms invariably are affected; symmetry is usual. Depigmentation may also appear in body sites remote from the chemical contact (e.g., axillae, genitalia, and torso). The process of depigmentation usually takes 2 to 4 weeks and may require up to 6 months of repeated contact to become visible. The fact that many exposed workers do not lose pigment indicates that host factors are important in susceptibility.

Table 5. Compounds known to cause hypopigmentation

o-Benzylchlorophenol (antiseptic)
p-Butylphenol (used in the manufacture of varnish and lacquer resins, as an antioxidant in soaps, and as a motor oil additive)
p-Cresol (disinfectant)
Hydroquinone and its monoethyl and monobenzyl ethers (used in black-and-white photoprocessing, in skin-lighteners, and as antioxidants in synthetic rubbers)
o-Phenylphenol (used as an agricultural fungicide, disinfectant, and in the rubber industry)
Pyrocatechol (topical antiseptic)
p-Tertiary butylcatechol (astringent)

Hyperpigmentation (also known also as melanosis or melanoderma) is due to accumulation of melanin from damaged melanocytes or to deposition of hemosiderin from extravasation of erythrocytes in the dermis. Another possible mechanism is overproduction of melanin by melanocytes in response to the offending agent. Hyperpigmentation is more likely to occur in dark-complexioned persons and can persist for years.

Common Etiologies

The cause of hypopigmentation is contact with alkylphenols (see Table 5, page 24), skin damage due to chemical and thermal burns, or blunt or repeated trauma to the skin. Hyperpigmentation typically follows a bout of dermatitis or other episode of inflammation. Coal tar pitch, creosote, and various aromatic chlorinated hydrocarbons are a few of the compounds that can stimulate overproduction of melanin. UV radiation-induced stimulation of melanin synthesis (tanning) is the most common cause of hyperpigmentation in dark-complexioned persons.

Diagnosis

Chemically induced hypopigmentation is indistinguishable from idiopathic vitiligo. Vitiligo affects about 1% of the general population and may be associated with autoimmune or endocrine abnormalities. Hypopigmentation must also be differentiated from depigmentation due to tissue destruction by chemical or thermal burns.

Hyperpigmentation should not be confused with birthmarks or direct skin staining or discoloration from contact with substances such as heavy metals (e.g., silver salts), nitrosylated compounds (e.g., nitric acid or dinitrophenol), derivatives of coal distillation (e.g., tar, pitch, and asphalt), and coal dust.

In most cases, the patient's history and physical examination are sufficient to diagnose cases of pigment alterations. The loss of melanin in light-complexioned persons can be detected by failure of the skin to fluoresce under a Wood's lamp.

- ☐ **Hypopigmentation may be the result of environmental exposures or of idiopathic vitiligo.**
- ☐ **Skin staining and birthmarks can be misdiagnosed as hyperpigmentation.**

Treatment

No effective treatment exists to reverse pigment changes. Hypopigmentation may last months to years after contact with the offending substance is discontinued, or it may be permanent. Depigmented skin should be protected from sunlight. Small depigmented areas may be camouflaged with agents such as Covermask, Dy-O-Derm, or Dermablend. Oral administration of psoralens and carefully graded UV radiation exposure (PUVA treatment) may be attempted if hypopigmentation involves large areas of skin.

In patients who have hyperpigmentation, worsening of the condition can be prevented by using sunscreens and covering affected areas

- ☐ **Hypopigmented and hyperpigmented areas should be protected from sunlight.**

with clothing, hats, and gloves. Topical bleaching creams prepared from hydroquinone or its monobenzyl ether must be used cautiously to prevent widespread depigmentation. A preparation consisting of 0.1% hydrophilic tretinoin (Retin-A), 5% hydroquinone, and 0.1% dexamethasone in a hydrophilic ointment has been used in a 5- to 7-week treatment regimen with some success.

Case 6 — Contact Urticaria

A 35-year-old woman consults you because of episodes of generalized hives that develop about 20 minutes after she uses certain brands of shampoo. The hives are preceded by sensations of itching, burning, and stinging of the skin on the scalp, upper face, and posterior aspect of the neck. The patient also experiences redness and tearing of the eyes, clear rhinorrhea, and nausea. She relates that a similar constellation of symptoms occurred after she applied an over-the-counter topical pain-relieving ointment for sunburn. A mild eczematous rash has been present on her forehead and posterior neck for about 6 weeks.

Challenge

(6a) What is the most likely cause of the patient's complaints?

(6b) What evaluation and testing might be helpful?

(6c) What treatment will most likely be effective?

Description

☐ **Contact urticaria is a skin reaction that appears immediately after contact with the offending agent.**

Contact urticaria is a localized wheal-and-flare response (hives) that develops almost immediately (a few minutes to about 1 hour) after direct contact with the eliciting agent. Many afflicted patients complain of skin sensations such as itching, burning, or tingling. Symptoms typically disappear within 24 hours.

Pathophysiology

☐ **Contact urticaria may be due to immunologic-, nonimmunologic-, or uncertain-mediated mechanisms.**

☐ **Anaphylactic reactions may occur in patients who have contact urticaria syndrome.**

Contact urticaria may be mediated by mechanisms classified as immunologic (allergic), nonimmunologic (nonallergic), or uncertain. Nonimmunologic urticaria, the most common type of contact urticaria, is caused by a direct action of the offending substance on the skin vasculature and a nonimmunologic release of vasoactive substances such as bradykinin, histamines, or other inflammatory mediators. The reaction remains localized.

Immunologic contact urticaria is an immediate allergic reaction in persons who have previously become sensitized to the offending agent. Parts of the skin that are remote from the contact site may be affected. The vasoactive effects in the immunologic form of contact urticaria are caused by an IgE-mediated reaction. The resulting erythema and edema are elicited mainly by histamines released from mast cells. Activation of the complement cascade and generation of anaphylatoxins can result in systemic effects (contact urticaria syndrome) in which the typical rash is accompanied by symptoms of asthma, rhinitis, conjunctivitis, orolaryngeal effects (itching and tingling sensations or edema of the lips, tongue, and mouth; or throat irritation), or gastrointestinal signs and symptoms. In rare cases, patients who have contact urticaria syndrome have experienced otherwise unexplained attacks of vascular collapse (anaphylactoid reactions).

The cause of the third type of contact urticaria is uncertain but includes both allergic and nonallergic mechanisms. Formaldehyde is an example of an urticant that has features of both types.

Common Etiologies

☐ **Latex rubber gloves are a common cause of immunologic contact urticaria.**

Immunologic contact urticaria is usually caused by proteins or protein complexes. It may also be caused by a wide variety of common chemicals, medications, cosmetics, and other agents (Table 6). The rubber in latex gloves is a common cause of contact urticaria among healthcare professionals, as is the cornstarch used in the gloves. Foodstuffs are also a common cause of contact urticaria. The orolaryngeal area is a site where immediate reactions are provoked by food allergens, most often among atopic persons.

Table 6. Some substances that cause allergic contact urticaria

Animal products
- dander
- hair
- saliva
- serum

Common Chemicals
- ammonia
- alcohol
- parabens
- polyethylene glycol

Cosmetics
- hair products
- nail polish
- perfumes

Foods
- eggs
- flour
- fruits & vegetables
- meats
- milk
- nuts
- seafood
- spices

Medications
- bacitracin
- cephalosporins
- chloramphenicol
- gentamicin
- neomycin
- salicylic acid

Plant products
- henna
- latex rubber
- papain
- strawberries
- woods

Textiles
- silk
- wool

Miscellaneous
- acrylic monomer
- epoxy resin
- formaldehyde
- nylon
- seminal fluid

Nonimmunologic contact urticaria has been provoked by contact with substances as diverse as acids (acetic, benzoic, butyric, cinnamic, sorbic), alcohols (ethyl and butyl), balsam of Peru, benzocaine, cinnamic aldehyde, cobalt chloride, dimethylsulfoxide, formaldehyde, witch hazel, sodium benzoate, and esters of nicotinic acid. Cold temperatures can also cause nonimmunologic contact urticaria.

Uncertain mechanism-mediated contact urticaria has been associated with exposure to ammonium persulfate, which is used to boost peroxide hair bleaches to achieve a platinum-blond effect. Sunlight, which can produce rapid development of a wheal-and-flare reaction in exposed areas, and aquagenic agents (water, saline, or the patient's own perspiration) are also associated with uncertain mechanism-mediated contact urticaria.

Diagnosis

Nonimmunologic contact urticaria must be differentiated from allergic contact urticaria and other forms of urticaria. The most important factor in making the correct diagnosis is taking a careful history of the relationship between possible exposures and development of symptoms. In cases of chronic urticaria, a clear cause is seldom identified.

☐ **A clear cause is seldom identified in cases of chronic contact urticaria.**

Patch or scratch/prick tests may be used with suspected etiologic agents. These tests should be used initially on normal areas of skin, then on involved skin (previously or currently affected) only when no reaction occurs on normal skin. Testing should be done by, or in consultation with, a dermatologist; resuscitation equipment and medications should be available in case a severe anaphylactoid reaction results.

Treatment

☐ **Antihistamines can alleviate symptoms of urticaria.**

Chlorpheniramine-like antihistamines are of value in treating urticaria. The newer agents that have less sedative effects, such as terfenadine (Seldane) and astemizole (Hismanal), are not as efficacious. (Note: Seldane and Hismanal are contraindicated in patients who are taking ketoconazole, itraconazole, erythromycin, or other medications known to impair the metabolism of Seldane or Hismanal, and in patients who have significant hepatic dysfunction.)

Nonsteroidal anti-inflammatory medications have proved useful in certain cases of nonimmune urticaria; however, they may cause anaphylaxis in patients who have immune urticaria, especially patients who exhibit the triad of asthma, nasal polyps, and rhinitis. These patients should be cautioned about the use of nonsteroidal anti-inflammatory agents. All patients suffering from urticaria should be advised to avoid further contact with the eliciting substance.

Case 7 — Malignant Neoplasms

A couple in their 60s who are native to a nearby rural area consult you because of the insidious development of a variety of skin lesions over the past 2 years. Both have hyperkeratotic lesions on the palms and the soles of the feet, as well as mottled-appearing hyperpigmented areas on the temples and neck. The man has a lesion on the right cheek that appears to be a basal cell carcinoma. Both patients complain of numbness and tingling in the feet and a general feeling of fatigue.

Challenge

(7a) Assuming that a single agent is responsible for the constellation of complaints of the couple, what sources should be investigated?

(7b) What treatment would you recommend?

Description

- ☐ **Skin cancer is the most common neoplasm in adults in the United States.**
- ☐ **Sunlight, either alone or in conjunction with other agents, is a major contributing factor to skin cancer.**
- ☐ **Reasons for the 700% increase in malignant melanoma in the past 60 years have not been well established.**
- ☐ **PAHs and inorganic arsenic are well-known causes of cancerous skin lesions.**

Cancer of the skin is the most common neoplasm among adults in the United States. More than 500,000 new cases of nonmelanoma skin cancer and about 28,000 cases of melanoma occur annually. Skin cancers associated with environmental factors include basal cell carcinoma, squamous cell carcinoma, malignant melanoma, and Bowen's disease (intraepidermal squamous cell carcinoma). Pre-nonmelanoma skin cancers, such as actinic keratoses, can also be induced by environmental factors.

Sunlight, either alone or in conjunction with other agents, plays an important role in the development of most skin cancers, especially malignant melanoma. The incidence of melanoma has increased more than 700% in the past 60 years. If the incidence continues to increase at the present rate, within the next decade a person's lifetime risk of developing melanoma will be approximately 1% (i.e., 1 case of melanoma per 100 persons). The reasons for this increased risk have not been well established but may be related to ozone depletion in the upper atmosphere; increased recreational sun exposure, especially early in life; increased use of industrial chemicals; and increased air pollution.

The usual wavelength in sunlight that causes skin cancers is 280 to 315 nanometers (UV-B). This range is capable of producing direct photochemical damage to the skin (e.g., alterations in DNA and other cellular constituents). UV-B also reacts with photoactive exogenous chemicals in or on the skin, causing them to absorb UV radiation and initiate or accelerate an adverse reaction in normal tissue. Industrial contaminants and air pollutants often contain photoactive chemicals, which can act as photosensitizers, additive carcinogens, or promotors.

The first association between occupational or environmental chemicals and malignancy was noted in 1775 by Percival Pott who reported a high incidence of scrotal cancer among London's chimney sweeps. Years later, it was discovered that the cancers were caused by exposure to certain polynuclear aromatic hydrocarbons (PAHs). PAHs are found in soot, pitch, creosote, petroleum, and oils such as cutting oil, mineral oil, and shale oil. (See *Case Studies in Environmental Medicine: Polynuclear Aromatic Hydrocarbon [PAH] Toxicity.*) Other chemicals found to be associated with skin tumors include phenolic compounds, aliphatic hydrocarbons, and inorganic arsenic compounds.

Inorganic arsenic compounds are known to cause a variety of skin lesions, including malignant neoplasms. Initial dermal manifestations of arsenic exposure may be mild erythema and hyperhidrosis of the palms and soles, followed by development of slightly raised, firm, generally symmetrical punctate keratoses. White-colored, nonraised hyper-keratoses may also develop on the ankles, shins, and dorsum of the hands. A diffuse hyperpigmentation of the skin interspersed with white, somewhat atrophic macules ("raindrops on a dusty road" appearance) may also be seen. Basal cell and squamous cell carcinomas may then develop. (See *Case Studies in Environmental Medicine: Arsenic Toxicity.*)

Bowen's disease, a squamous cell carcinoma, may arise spontaneously in situ or may develop after chronic exposure to inorganic arsenic or other chemicals. Bowen's disease consists of randomly distributed, sharply demarcated, erythematous, scaling lesions that range in size from a few millimeters up to 1 to 2 centimeters in diameter. The lesions grow slowly and rarely metastasize.

Pathophysiology

Many chemical substances associated with malignant neoplasia are thought to interact directly with cellular macromolecules, resulting in neoplastic transformation of the affected cell. In some cases, absorbed chemicals are converted by skin enzymes (specifically, aryl hydrocarbon hydroxylases) to forms that then combine with DNA and other cellular constituents. Arsenic is thought to inhibit the enzymes involved in DNA replication and repair.

Some chemical agents act either concomitantly (cocarcinogens) or serially (promoters) to cause neoplastic transformation. In many cases, precancerous lesions, such as actinic or arsenical keratoses and tar warts, may precede the development of frank cancerous lesions. A latency period of several decades may lapse between exposure to a carcinogen and appearance of a cancerous lesion.

- ☐ **The latency period for development of cancerous lesions can be 20 years or more.**

Common Etiologies

Certain chemical agents, such as PAHs and inorganic arsenic, are known to cause skin cancer. Nonchemical agents that may cause malignant neoplasms include sunlight, ionizing radiation, and physical trauma. Sunlight is the most important cause of malignant melanoma.

- ☐ **Sunlight is the most important cause of malignant melanoma.**

Diagnosis

All potentially cancerous skin lesions must be differentiated from benign lesions. Suspected malignant skin lesions are diagnosed most accurately by histologic examination of excisional biopsies. A punch biopsy of suspect lesions may also be performed.

- ☐ **Diagnosis of a malignant skin lesion requires a biopsy.**

Treatment

☐ **Treatment of skin cancer depends on whether the cancer is localized or is metastasizing.**

Prevention is the first line of defense for skin cancer. Avoiding overexposure to sunlight is most important. Protection from UV radiation can be accomplished by wearing tightly woven clothing and wide-brimmed hats and by applying sunscreens as absorbers. Sunscreens, which contain p-aminobenzoic acid (PABA) derivatives to absorb UV rays, can provide sun-protective factors (SPFs) ranging from 2 to 50 or more. An SPF of 15 allows most persons to remain out of doors for 5 hours before developing minimal erythema. Light-complexioned persons, persons of Celtic origin (i.e., Scotch, Irish, Welsh), and those with certain conditions (e.g., albinism, xeroderma pigmentosum, and erythropoietic protoporphyria) appear to be at increased risk for developing skin cancer. These sensitive populations may require more potent sunscreens.

Surgical excision and radiation are the most common treatment modalities for localized malignant skin lesions. All excised tissue should be sent for histologic examination to confirm the diagnosis and to be certain that an adequate margin of normal skin was removed. Surveillance for the development of further skin cancers should be continued. The treatment of metastasizing skin cancers or lesions with extensive local infiltration is beyond the scope of this review. Patients who have malignant tumors should be referred to, or treated in consultation with, a physician knowledgeable in cancer therapy.

Diagnostic Procedures

Obtaining and recording a detailed history of exposures (workplace, home, and environment) is essential in diagnosing skin disease. Besides physical examination, several special techniques may aid in the diagnosis of skin lesions. These include patch tests to detect contact allergy, skin biopsy, cultures, and microscopic scrapings of skin to detect yeasts, fungi, parasites, and fibrous glass. Referring patients to, or consulting with, a dermatologist who can perform or interpret dermatologic diagnostic testing, may be advisable.

Patch Testing

Patch testing is frequently used to differentiate between allergic contact dermatitis and other forms of dermatitis. The presence of a delayed hypersensitivity reaction to an offending substance can be determined by placing a suitably prepared, nonirritating amount of a sample on the skin (usually on the back) under a chamber or impervious bandage (patch). If an eczematous dermatitis lesion develops under the patch during the 48 hours after application, allergy to the test substance or to an antigenically similar cross-reacting substance can be inferred. If no reaction is evident, the patches are removed, and the sites are reexamined for delayed reaction at 72 and 96 hours after application.

☐ **Patch testing can help differentiate allergic from other forms of dermatitis.**

Interpretation of patch testing is often difficult, and it is usually recommended that the testing be carried out in specialized centers or by consultants who routinely do patch testing. If no response is provoked, it does not mean unequivocally that the patient is not allergic. For example, if an offending or cross-reacting substance was not included, or was not applied in proper concentration, a false-negative result will occur.

Complications of patch testing include the "angry back syndrome," in which the patient's entire back becomes edematous and erythematous. Flare-up of previously existing eczema can also occur, especially when testing materials are not obtained from standard commercial sources. Even local response to the test substance may be extensive, causing patient discomfort. Patch testing itself can result in allergic sensitization to a substance to which the patient was not allergic previously, although this is a rare occurrence. Infections, scarring, and pigment alterations may also be complications of patch testing.

Photopatch Testing

When photosensitivity dermatitis is suspected, a combination of chemical patch testing and special light exposure may reveal the cause. Duplicate patches are used; one set is covered, and the other

☐ **Photopatch testing may help reveal the cause of photosensitivity dermatitis.**

set is exposed to a measured amount of UV radiation. There are several difficulties in the performance and interpretation of photopatch testing, and it should be performed by practitioners who have experience and the requisite special equipment.

Skin Biopsy

☐ **Skin biopsy is not helpful in differentiating allergic contact dermatitis and irritant contact dermatitis.**

The appropriate skin biopsy (punch biopsy or excision of the lesion) usually can be performed under local anesthesia by experienced practitioners in an outpatient setting. Microscopic examination of the specimens obtained can allow differentiation between benign and malignant skin conditions. Irritant and allergic contact dermatitis cannot be readily differentiated on routine skin biopsy.

Other Diagnostic Procedures

☐ **Skin scrapings, UV-light examinations, cultures, and serologic testing are diagnostic tools used for various skin lesions.**

Other procedures include skin scrapings, UV-light examinations, cultures, and serologic testing.

Skin scrapings can be used to look for fungal hyphae, for strands of fiberglass in suspected fibrous glass dermatitis, or for scabies mites and eggs. A Wood's lamp, which produces UV radiation, can be used to examine suspected areas of hypopigmentation in light-complexioned persons. Areas deficient in melanin will not fluoresce under UV light, whereas areas of skin with normal melanin content will fluoresce.

Bacterial, viral, or fungal cultures may be indicated if dermal infections are considered in the differential diagnosis. Crusts, when present, should be lifted with a scalpel blade before swabbing the lesion with a sterile cotton-tipped applicator to obtain material for bacterial cultures. Fungi may be collected for culture media by gently scraping the skin with a sterile scalpel blade. Viral cultures from skin lesions require specialized laboratory facilities. Viruses can be collected for special media by unroofing lesions and swabbing with a sterile cotton-tipped applicator.

Patients who have immunologic-mediated contact urticaria may be evaluated by serologic testing. Protein electrophoresis and measurement of circulating IgE may be useful.

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Sources of Information

More information on skin lesions and treating and managing cases involving skin lesions due to environmental exposure can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Skin Lesions and Environmental Exposures—Rash Decisions* is one of a series. To obtain other publications in this series, please use the order form on the inside back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of the Director, at (404) 639-6204.

Answers to Pretest and Challenge Questions

Pretest questions are on page 1. Challenge questions begin on page 3.

Pretest

The Pretest questions (a) and (b) are answered in Challenge answers 1, 2, 3, and 6 below.

Challenge

(1a) The man in Case No. 1 has most likely developed an irritant contact dermatitis from the insulating material (e.g., fiberglass, rock wool). This possibility could be investigated by placing skin scrapings on a microscope slide with 1 to 3 drops of 10% potassium hydroxide (KOH) and examining the specimen under a light microscope using low power. The presence of fibrous strands would confirm the diagnosis. Dermatitis elicited by fibrous glass is variable and depends on individual characteristics and extent of exposure.

(1b) The woman probably has either irritant or allergic contact dermatitis. The basic histopathologic appearance of these two conditions is essentially the same, and differentiating between them by appearance or routine skin biopsy is difficult. However, most paint-stripping products contain one or more of the following compounds: isopropyl alcohol, cresylic acid, methylene chloride, glacial acetic acid, aliphatic hydrocarbons, and aqueous ammonia, all of which tend to be irritants rather than allergens. The presence of mild rather than severe itching, more erythema than vesiculation, localized lesions, and insidious rather than explosive onset are more consistent with irritant contact dermatitis than with allergic contact dermatitis.

(1c) Both the man and the woman should be advised to avoid exposure to the offending substances, at least temporarily. Applying and rapidly removing adhesive or Scotch tape from the man's affected skin may remove the fibers and help relieve the itching.

The contact dermatitis of both patients may be treated using Domeboro's solution (1:40 dilution) or Burow's solution. Dressings soaked with one of these solutions should be applied topically for 15 to 20 minutes, 6 times daily. Topical corticosteroids may be applied, starting with a steroid of low potency and progressing to more potent corticosteroids as needed. Mild sedatives and antihistamines may be administered to relieve itching. Topical or systemic antibiotic therapy may be used to combat secondary bacterial infection. Repeated exposure to UV radiation may be therapeutic in some cases, causing hardening or increased resistance to further irritation.

(2a) The rash of the patient in Case No. 2 is not likely to be due to airborne allergens or irritants in the new office location. Although some cases of allergic or irritant contact dermatitis can develop from exposure to airborne allergens or irritants, the patient's occupational history and the location of the rash do not suggest this etiology. Eyelids, cheeks, nasal folds, and the neck most probably would be involved if an airborne agent in the workplace were responsible. The hand and wrist location suggests contact with an allergen that is handled.

(2b) Yes, the patient's woodworking hobby, with recent introduction of various exotic woods and Japanese varnish (possibly derived from the Japanese lacquer tree), suggests a cross-sensitivity reaction to agents related to *Rhus* plants, to which he is known to be sensitized.

(2c) The patient probably has allergic contact dermatitis. Therapy would be identical to the regimen for irritant contact dermatitis described in (1c) above. Attempts to desensitize sensitive persons have been unsuccessful in most cases.

(3a) Given the rural location and outdoor activities in which the children in Case No. 3 were involved, airborne allergic contact dermatitis to *Rhus*-type plant oleoresins (e.g., poison ivy, poison oak, poison sumac) or pollen could be the cause. However, vesiculation would be expected with allergic contact dermatitis. Patch testing could rule out this diagnosis.

Puncturing lime skins while making sachets during craft class could have exposed the children to psoralens, which are known photoirritants. Immediately after the craft class, the children engaged in outdoor sports. This combination of activities could lead to photosensitivity dermatitis. Because the counselors were involved in a staff meeting during the craft class and did not puncture the limes, only the children were affected.

(3b) One of the most important components in therapy for photoreactions is identification and avoidance of the photoactive agent. When exposure to the offending agent cannot be avoided, sunlight exposure should be minimized. Light exposure can be reduced by wearing protective clothing such as broad-brimmed hats, long sleeves, and tightly woven fabrics, or by using sunblocking agents. Symptomatic topical treatments may also be used.

(4a) The rash of the patient in Case No. 4 is more consistent with chloracne than with acne vulgaris. Acne vulgaris has a different appearance, and its distribution is typically the central face, back, and chest; it seldom affects the buttocks. The sebaceous glands are usually active in acne vulgaris, but chloracne gives the skin a "dry" appearance. Comedones are small in size and number in cases of acne vulgaris, whereas typical straw-colored cysts are almost pathognomonic for chloracne.

The patient's occupation is a potentially relevant factor. A telephone call to a manager at the utility company reveals that old heat exchanger fluids contain PCBs, and in the process of replacing these fluids with less hazardous materials, the workers could have accidental contact with the material. The finding that PCBs are the most probable cause of the patient's chloracne should prompt a health hazard evaluation by the appropriate regulatory authorities and should encourage action to prevent further exposure.

(4b) The chloracnegenic agent should be identified and exposure stopped. Chloracne is resistant to treatment in many cases. Medications used for acne vulgaris are ineffective for chloracne, but oral and topical antibiotics, acne surgery, injection of inflammed cysts with triamcinolone, and dermabrasion of scars may be efficacious. Topical application of retinoic acid (Vitamin A) or 13-cis-isoretinoic acid (Accutane) has been used on carefully selected patients with some success. In addition to treating the skin lesions, examination and testing should be performed to rule out hepatotoxicity, porphyria cutanea tarda, and peripheral neuropathy—all possible systemic effects of PCB exposure. (For further information, see *Case Studies in Environmental Medicine: Polychlorinated Biphenyl [PCB] Toxicity.)*

(5a) Yes, the manufacturing plant could be associated with the children's skin lesions in Case No. 5. A similar outbreak among workers at a manufacturing facility and children in a neighboring school was reported in 1985; a powdered thiadiazole was responsible in that case. Because an etiologic agent for the pigment changes in the children has not been found in routine testing of the water and food at the school, it would be advisable to consider other common sources in the neighborhood, such as the school playground. The nearby chemical manufacturing facility should also be investigated as a possible source, especially because the parents of the two children with more severe manifestations are employed at this plant. The parents could be carrying contamination home on their skin, clothing, and shoes. In addition, the children may be playing in an area with contaminated soil.

(5b) You could begin your investigation by contacting the nurse or health and safety manager at the parent's workplace to determine whether a workplace agent or process is associated with the rashes of some workers. You could request from the manufacturer Material Safety Data Sheets (MSDSs) or other information about the raw materials, byproducts, chemical intermediates, and finished products used or produced at the plant.

The Toxic Chemical Release Inventory (TRI), which is maintained by the U.S. Environmental Protection Agency (EPA) and is available to the public either online through the National Library of Medicine or on CD-ROM, could be used to determine the normal releases from the plant. Plant management, the local EPA, or the local fire department could be consulted to determine whether any accidental chemical releases have occurred recently at this facility. If soil contamination is suspected, soil samples from nearby playgrounds, school yards, or other play areas should be tested. Local or state health officials may be contacted for assistance.

(5c) If the lesions are persistent, large, and cosmetically displeasing, you could refer the children to a dermatologist for consideration of PUVA treatment. Sunscreens and protective clothing can protect areas with depigmented skin and prevent hypopigmentation from worsening.

(6a) The constellation of complaints of the patient in Case No. 6 is consistent with contact urticaria syndrome. Balsam of Peru and various alcohols (especially propyl alcohol and ethyl alcohol) in numerous consumer cosmetic products and benzocaine in many over-the-counter topical analgesic preparations could be causative agents.

(6b) Evaluation might include correlating the history of the illness with probable exposures, serologic studies of circulating IgE, and patch or scratch testing (performed by, or in consultation with, a dermatologist in a setting with resuscitation equipment in case of anaphylactoid reaction).

(6c) Usual treatment for contact urticaria includes advice to avoid suspected or known causative substances and administration of antihistamines. In certain patients, nonsteroidal anti-inflammatory medications have shown some efficacy.

(7a) The constellation of complaints of the couple in Case No. 7 suggests chronic arsenic poisoning. Arsenic toxicity from criminal activity, intentional surreptitious self-injury, occupational exposure, and environmental exposure should be investigated.

On questioning, the couple reveals that they have obtained drinking water from a private well for the past 40 years and that they heat their home with a wood stove fueled with scrap wood. Analysis of the well water reveals arsenic at 0.62 milligrams per liter (mg/L), a concentration significantly above the EPA maximum contaminant level (MCL) of 0.05 mg/L. Ashes collected from the wood stove and soot from the chimney also contain arsenic in concentrations of several hundred parts per million; the most likely source of this contamination is arsenic-containing preservatives in the scrap wood.

(7b) Initial action should be taken to terminate further arsenic exposure; it will be futile to treat the skin lesions (or provide chelation therapy to reduce body burden) if exposure continues. An alternative source of drinking water should be substituted immediately, contaminated lumber should not be burned, and the home should be decontaminated. Advice on abatement and remediation and aid in investigating any other possible sources of arsenic may be obtained from the state or local health department. (For further information on arsenic and arsenic poisoning, see *Case Studies in Environmental Medicine: Arsenic Toxicity.)*

Treatment of the man's basal cell carcinoma may involve radiation therapy or excisional biopsy, including a suitable margin of normal-appearing skin. All tissue removed should be submitted for histologic confirmation of diagnosis and to be certain the tissue borders are free of cancerous cells. The patient should be counseled to avoid prolonged exposure to sunlight and to use sunscreens or protective clothing whenever exposure to sunlight is anticipated.

*Glossary**

anaphylaxis. Commonly used to denote the immediate, transient kind of immunologic (allergic) reaction characterized by contraction of smooth muscle and dilation of capillaries due to release of pharmacologically active substances (histamine, bradykinin, serotonin, and slow-reacting substances), classically initiated by the combination of antigen (allergen) with mast cell-fixed, cytophilic antibody (chiefly IgE).

acne mechanica. Acne caused or exacerbated by friction.

acne medicamentosa. Acne caused or exacerbated by several classes of drugs including antiepileptics, halogens, and steroids.

acne venenata. Acne produced by external irritants or drugs internally administered.

acne vulgaris. Simple acne, probably caused by hormonal fluctuations.

bullae (singular bulla). Large bubble-like structures (vesicles) appearing as a circumscribed area of separation of the epidermis from the subepidermal structure, typically filled with serum.

chloracne. Acne-like eruptions due to prolonged contact with certain chlorinated aromatic hydrocarbon compounds.

chloracnegenic agents. Substances that cause chloracne.

comedones. A plug of sebaceous matter, capped with a blackened mass of epithelial debris, filling the pilosebaceous orifice.

dermatitis. Inflammation of the skin.

> **atopic d.** Characterized by the distinctive phenomena of atopy, a Type I allergic reaction, specifically one with strong familial tendencies, caused by allergens such as pollens, foods, dander, and insect venoms, and associated with the Prausnitz-Küstner (IgE class) antibody.
>
> **allergic contact d**. A delayed type of induced sensitivity (allergy) of the skin with varying degrees of erythema, edema, and vesiculation, resulting from cutaneous contact with a specific allergen.
>
> **irritant contact d**. Irritation of skin caused by contact with substances that are toxic to epidermal or connective tissue cells; lesions are usually erythematous and papular, but can be purulent or necrotic, depending on the nature of the toxic material applied.

dermatomyositis. A progressive syndrome characterized by muscular weakness with a purplish erythematous skin rash on the face.

eczema. Generic term for acute or chronic inflammatory conditions of the skin, typically erythematous, edematous, papular, vesicular, and crusting; often followed by lichenification and scaling and occasionally by duskiness of the erythema; often accompanied by sensations of itching and burning.

erythema. Inflammatory redness of the skin.

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*Adapted from *Stedman's Medical Dictionary*, 25th edition, Baltimore: Williams and Wilkins, 1990. Modified with permission from Williams and Wilkins.

erythema multiforme. An acute eruption of macules, papules, or subdermal vesicles presenting a multiform appearance, the characteristic lesion is typically over the dorsal aspect of the hands and forearms; its origin may be allergic, seasonal, or from drug sensitivity, and the eruption may be recurrent or may run a severe course (Stevens-Johnson syndrome), possibly ending in death.

excipient. An inert substance such as gum arabic, syrup, lanolin, or starch, that acts as a diluent or forms a vehicle for drug delivery.

folliculitis. An inflammatory reaction in hair follicles; the lesions may be papules or pustules.

exfoliative dermatitis. General scaling of the skin, usually with erythema.

hapten. Incomplete or partial antigen; an antigen that is incapable, alone, of causing the production of antibodies.

hives. See urticaria.

hyperkeratosis. Hyperkeratinization; hypertrophy of the horny layer of the epidermis.

hyperpigmentation. Increased pigmentation of the skin.

hypertrichosis. Growth of hair in excess of normal.

hypopigmentation. Decreased pigmentation of the skin.

keratosis. Any lesion on the epidermis marked by the presence of circumscribed overgrowths of the horny layer.

lichenification. Leathery induration and thickening of the skin with hyperkeratosis, due to a chronic inflammation caused by scratching or long-continued irritation.

leukoderma. An absence of pigment, partial or total, in the skin.

macular. Relating to or marked by a small, discolored patch or spot on the skin, neither elevated nor depressed below the skin's surface.

malar crescent. Around the cheek or cheekbones.

melanin. Pigment that occurs in the hair, skin, or retinas.

melanocytes. Pigment cells of the skin.

melanoderma. An abnormal darkening of the skin by deposition of excess melanin, or of metallic substances such as silver and iron.

melanoma. A malignant neoplasm derived from cells that are capable of forming melanin, which may occur in the skin of any part of the body; in the early phases, the lesion is characterized by proliferation of cells at the dermal-epidermal junction, and the neoplastic cells soon invade adjacent tissue extensively. Melanomas frequently metastasize widely; most examples of this neoplasm occur in adults and may originate de novo or from a pigmented nevus or malignant lentigo.

milia (singular *milium*). Sebaceous tubercle; whitehead; a small subepidermal keratin cyst, usually multiple, therefore commonly referred to in the plural.

miliaria. An eruption of minute vesicles and papules due to retention of fluid at the mouths of the sweat follicles.

nummular. Marked by circular or oval lesions.

papules. Small, solid elevations on the skin.

photoallergy. Sensitization of the skin to light.

phototoxicity. The condition arising from overexposure to ultraviolet light.

pruritis. Itching.

psoralens. Furo[3, 2-g]coumarin; a phototoxic chemical derived from fruits of the citrus family (e.g., limes).

psoriasis. A condition characterized by the eruption of circumscribed, discrete and confluent, reddish, silvery scaled macropapules.

Rhus. A genus of trees and shrubs (family Anacardiaceae) containing various species that are used for their ornamental foliage; poison ivy, poison oak, and poison sumac belong to this genus.

solar elastosis. Degenerative change in elastic tissue of the dermis due to repeated or constant exposure to sunlight over a period of years.

urticaria. Hives; an immediate eruption of itching wheals, which may be due to physical and chemical agents, foods or drugs, foci of infection, or psychic stimuli.

urticaria syndrome. Consists of the typical urticarial rash with systemic involvement.

vesiculation. Blistering.

vitiligo. The appearance on the otherwise normal skin of loss of melanin pigment with white patches of varied sizes, often symmetrically distributed; the skin bordering the affected sites is usually hyperpigmented, and hair in the affected areas is usually white.

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Acoustic Trauma Caused by the Telephone

Report of Two Cases

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Key Words. Acoustic trauma · Temporary threshold shift · Cord-type telephone · Cordless telephone

Abstract. Two patients with acoustic trauma resulting from the use of telephones have been evaluated. Both patients used a particular type of telephone which had the ringing device located in the ear receiver and no automatic gain control in the circuit. The output of the bell recorded on one of these telephones was in the 139-dB range on the A scale. The auditory insult resulted, in the case involving a cord-type telephone, from the transmission of a loud, extraneous sound probably due to a misfunction of the circuit and, in the second case, from the patient holding his cordless telephone against his ear when ringing occurred.

Acoustic traumata resulting from the use of cordless telephones have recently been reported. These telephones, in order to save space and weight, have the ringing device located within the ear receiver. There is no limiting circuit or automatic gain control either in the ringing device or in the earpiece transducer. Singleton et al. [1] reviewed 33 cases of hearing loss due to acoustic trauma from cordless telephones, cases collected either by him or by other members of the American Academy of Otolaryngology-Head and Neck surgery (AAO-HNS). In 30 patients the auditory insult resulted from the individual picking up the telephone when it was ringing and placing it to his ear without switching to the 'talk' mode. However, 3 patients used the telephone correctly; the injury resulted from a loud, extraneous crack sound which occurred while the telephone was used in the 'talk' mode. Most of these patients suffered from a permanent sensorineural hearing loss predominant in the low and midfrequencies. Subsequent reports have supported Singleton's observation concerning this type of acoustic trauma [2, 3].

In Switzerland, the Federal Constitution has attributed the monopoly of telecommunications to the National Post-Telegram-Telephone Agency (PTT) [4]; only four accredited manufacturers provide telephones for the entire country and cordless tele-

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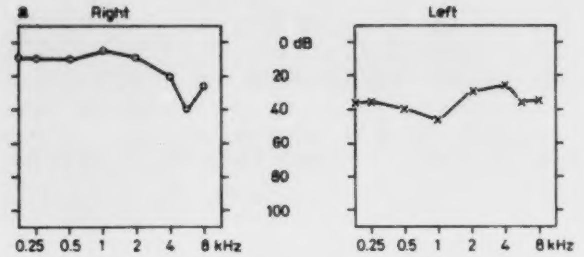

b

Hz	250	500	1,000	2,000	4,000
Ipsi		85	85	90	
Contra	85	90	90	95	95
Reflex decay (1,000 Hz) : no					

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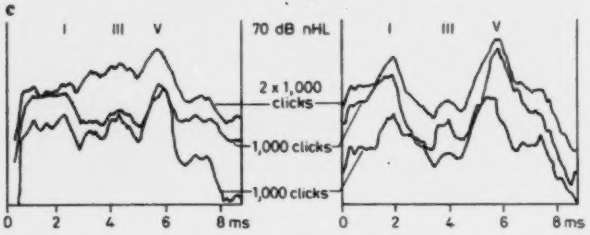

Fig. 1. Audiometrical results of the first patient suffering from an acoustic trauma due to a loud sound transmitted by a cord-type telephone. **a** Pure-tone audiogram. **b** Thresholds and decay of the stapedial reflex. **c** ABR (right ear on the left, left ear on the right). The audiogram shows a low and midfrequency sensorineural hearing loss of the left ear. The thresholds of the stapedial reflex are normal as well as the interwave intervals and amplitude ratios of the ABR.

phones are officially prohibited. Standards for maximum peak acoustic power (120 dB) are based on advice edicted by the International Telegraph and Telephone Consultative Committee (ITTCC). This present regulation is strict and thereby the 'Caisse Nationale suisse d'Assurance en cas d'accident' (National Insurance Company for Accidents, CNA) has not been notified of any case of hearing loss resulting from the use of telephones during the last two decades. However, in the past few years, unofficial telephones have become available on the market, thus escaping control by the PTT.

We report two cases of hearing loss in individuals using these unofficial devices. In 1 patient the auditory insult resulted from the transmission of a loud, extraneous crack sound by a cord-type telephone: this is the first case report of trauma caused by a noncordless telephone.

Case Report

Case 1

A healthy 56-year-old woman was referred to the ENT Department of the University Hospital of Geneva on October 28, 1986. She had been treated for 3

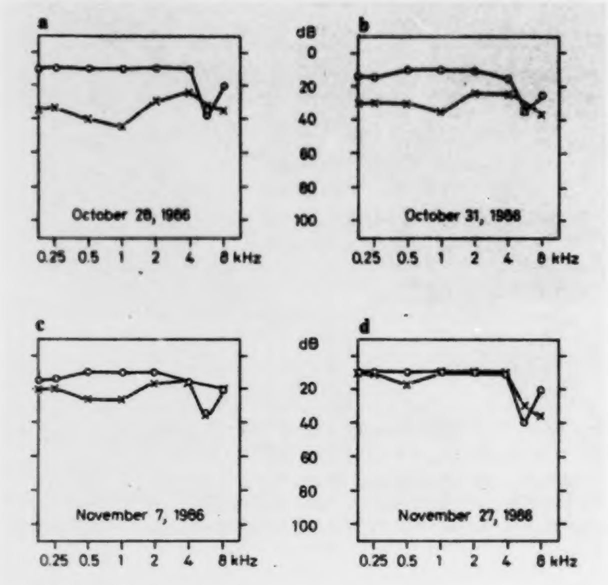

Fig. 2. Hearing thresholds of the first patient measured 6 h after the trauma (**a**), 3 days (**b**), 10 days (**c**) and 30 days after the trauma (**d**). The successive audiograms show the recovery of the hearing deficit due to a telephone-induced acoustic trauma within 4 weeks.

years for an idiopathic hypothyroiditis. That morning, she heard a loud crack sound in her left ear when answering the phone. She immediately complained of hearing loss and tinnitus in her left ear. The pitch of the tinnitus was subjectively comparable to the damaging noise perceived. The first audiometric evaluation was performed 6 h after the trauma occurred. The pure-tone audiometry demonstrated a midfrequency sensorineural hearing loss between 0.125 and 2 kHz. The auditory brainstem responses (ABR) showed normal interwave intervals and amplitude ratios. The thresholds of the stapedial reflex were normal (fig. 1) as well as the electronystagmography with caloric testing.

The tinnitus disappeared spontaneously after 3 days and her hearing gradually improved, with complete recovery within 4 weeks (fig. 2). The review of the cord-type telephone used by this patient revealed that it was made to receive several calls at the same time, and, like cordless units, had the ringing device located in the ear receiver. The ringing lasted 1 s. The peak impulse sound level of the ring was recorded on the A scale, using a standard 6-cm^3 coupling for SPL (Bruel & Kjaer (B&K) 4152) connected to a B&K type

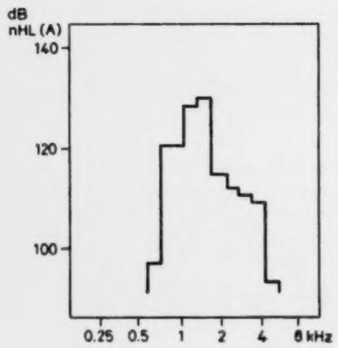

Fig. 3. Peak impulse sound of the ring of the cord-type telephone having caused the acoustic trauma in the first patient. The intensity of the ring of the cord-type telephone has been measured on the A scale using a standard 6-cm^3 coupling for SPL (B&K 4152). The peak impulse sound reached 139.5 dB between 1 and 2 kHz.

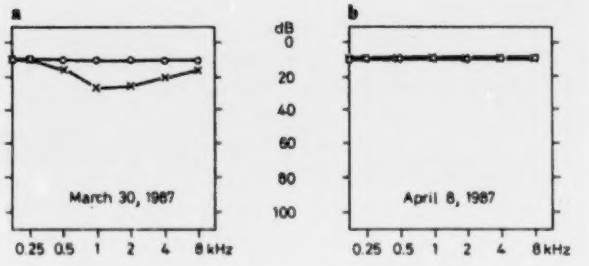

Fig. 4. Audiometrical results in the second patient who experienced acoustic trauma after exposure to the ring of a cordless telephone. **a** Audiogram obtained 3 weeks after the trauma showing a midfrequency sensorineural hearing loss of the left ear. **b** Audiogram obtained 4 weeks after the trauma showing the recovery to normal hearing 1 week later.

4145 1" condenser microphone and a B&K sound level meter type 2218; it ranged from 134 dB in the 'low talk' position to a high of 139.5 dB in the 'high talk' mode. The fundamental frequency of this unit was 1,500 Hz (fig. 3). It was not possible to reproduce experimentally the extraneous crack sound heard by the patient.

Case 2

This young man was first seen in our ENT Department on April 6, 1987. Three weeks before, when using a cordless telephone, he omitted to switch to the 'talk' mode so that the bell rang directly into his left ear. He complained of an immediate hearing loss and tinnitus. The tinnitus disappeared within a few days. He noticed an improvement in his hearing level within 3 weeks but without complete recovery: he then came in for a medical visit. The pure-tone audiometry showed a midfrequency sensorineural hearing loss predominant between 1 and 2 kHz. The thresholds of the stapedial reflex and the electronystagmogram were normal. A second pure-tone audiometry, done 4 weeks after the acoustic trauma, revealed a normal hearing level (fig. 4).

Discussion

The midfrequency sensorineural hearing loss observed in both patients resembles the findings obtained in most of Singleton's patients [1] emphasizing that a characteristic hearing loss results from this particular type of acoustic trauma. One case of significant loss in discrimination score without any significant change in pure-tone audiometry has been reported [3].

The hearing loss caused by cordless telephones results most frequently from the patient neglecting to switch from the normal 'standby' position to the 'talk' mode before placing the receiver to the ear so that the audiodevice will not continue to ring directly into the ear. In some instances, the injury has been reportedly caused by the transmission of a loud, extraneous crack noise likely resulting from a misfunction of the circuit of the phone. The case of our first patient illustrates that, although less frequent, this accident may also occur with cord-type telephones. The peak impulse sound level of the ringing was recorded up to 139.5 dB; it seems reasonable to assume that the accidental noise was transmitted at similar intensities. Such intensities are known to have a damaging effect on the inner ear. Most experimenters agree that mechanical factors are responsible for damage to the sensorineuroepithelium at sound intensities higher than 120 dBA [5].

It is likely that other physicians have seen one or more isolated cases but have not picked up on the midfrequency hearing loss, or paid any particular attention to them and therefore have not reported the cases. These accidents may easily be misdiagnosed as beginning Menière's disease or sudden deafness due to viral infection.

The typical acoustic trauma notch in the 3- to 6-kHz range is not a common finding in this group of patients. This unfortunate experience with human subjects illustrates the findings of many experimental studies documenting the relation between maximum stimulation and maximum damage positions along the organ of Corti [6–8] by using pure tones or narrow band noises as stimuli. The morphological substrate underlying temporary threshold shifts (TTS) has been extensively studied with some controversial results. TTS may be detected without any significant ultrastructural change suggesting a metabolic disturbance; more intense stimulations result in temporary swelling of dendrites to inner hair cells. The resulting TTS lasts for several hours [9]. Vascular disturbances in the pathogenic sequences after an acute noise exposure have also been reported [10–13]. Changes in microcirculation may still be present 3 weeks after short-term and mild noise exposure [13]. In the light of the most recent studies, at the electron microscopy level, more subtle and consistent changes have been described. The most common finding observed in several different animal models [14–16] is depolymerization of the actin filaments at the base of the hair cells stereocilia reducing their stiffness which returned to normal within 6 weeks after exposure [16].

It is imperative that physicians and audiologists become aware of the potential hazard that telephones may produce under certain circumstances. The greatest danger results from telephones (cordless or not) in which the ringing device is located in the ear receiver. For this reason, these telephones should be prohibited. Unlike the patients of Singleton et al. [1] or Orchick et al. [2], our 2 patients have fortunately recovered normal hearing; however, such a favorable outcome is not always predictable and, at the present time, no treatment is known for reestablishing normal hearing after acoustic trauma.

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Behavioral and Audiological Manifestations of Noise-Induced Hearing Loss

Sufficiently intense sounds have the potential of disrupting all parts of the peripheral and central auditory system. Noise can have direct mechanical effects on the middle ear, such as ossicular and discontinuity, tympanic membrane perforation, or fistula of the oval window, and on cochlear structures. The outer hair cells are particularly vulnerable to the effects of excessive noise exposure, followed in vulnerability by the inner hair cells. The cochlea, once damaged, cannot be repaired; the subsequent loss of sensory cells and neural changes produces an auditory pathology that represents the morphologic substrate for the loss of hearing threshold, referred to as a noise-induced sensorineural hearing loss, or simply a noise-induced hearing loss (NIHL). A similar set of cochlear changes can be induced by lower levels of noise that continuously stress the metabolic processes of the cochlea. While these changes may initially produce a temporary loss of threshold, with repeated exposures they may lead to permanent changes.

Hearing loss resulting from noise exposure can be separated into three distinct categories: acoustic trauma, temporary threshold shift (TTS), and permanent threshold shift (PTS). A single, relatively intense noise exposure is referred to as an acoustic trauma and is usually followed by tinnitus and a change in hearing threshold. While hearing may improve slightly over time, if the exposure is sufficiently intense a PTS will result. One or both ears may be involved. Those who experience an acoustic trauma may also suffer from tympanic membrane perforation(s) and disarticulated or fractured ossicles. Such middle-ear disorders are more likely to appear, if at all, once the peak noise exposure level exceeds approximately 160 dB SPL. In general, however, any acute sound exposure that causes any of the following symptoms represents a hazard to the auditory system and could result in an acute acoustic trauma: immediate pain, a tickling sensation in the ears often occurring if the SPL exceeds approximately 120 dB, vertigo, tinnitus, hearing loss, or reduced communication skills.

Lower levels of noise (<85 dB[A]) are potentially hazardous and may result in an NIHL if, following exposure, there is a transient shift in the threshold of hearing that recovers gradually (a TTS). While the onset of hearing loss in acute acoustic trauma is instantaneous, the onset and progression of NIHL is far more insidious since it accumulates, usually unnoticed, over a period of many years of exposure to noise on a daily basis. During the initial stages of NIHL, the temporary hearing loss recovers within a few hours or days following removal from the noise. However, if the exposure to this noise is repeated often enough, the hearing loss may not recover completely (that is, permanent sensorineural hearing impairment will begin).

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The following is a typical case history of an history individual with permanent NIHL:

> A 48-year-old man had chief complaints of constant, high-pitched tinnitus and progressive hearing loss in both ears over the previous 2 years. He reported some difficulty hearing in quiet surroundings but noticed marked difficulty understanding speech in noisy environments. He did not report any previous serious illnesses, accidents, atypical drug use, or problems with his ears. For the past 8 years, he had worked in a noisy textile mill, where he said that he "occasionally" wore hearing protective devices. The patient had not been exposed to other hazardous noises off the job, such as gunfire or motorbikes.

The diagnosis of NIHL comes under the domain of the audiologist, whose primary responsibility is the identification and measurement of hearing loss and the rehabilitation of those with hearing impairment. By measuring auditory thresholds in decibels (relative to a normal hearing level or 0 dB HL) for pure tones as a function of frequency, an audiogram (a frequency-intensity graph) is generated. *Hearing level (HL)* is a term used to designate an individual's hearing threshold at a given test frequency, referenced to an audiometric zero level. The audiogram will help answer the following questions: (1) Is there evidence of hearing loss? (2) If so, what is the severity of the loss? (3) What is the nature of the loss (conductive, sensorineural, or mixed)? and (4) Can the use of a hearing aid(s) benefit the hearing-impaired individual? A typical normal audiogram and an audiogram from an individual with an NIHL are shown in Fig. 16-5.

Hearing loss induced by most industrial noise characteristically produces a bilateral symmetrical loss that is progressive in nature so long as the individual is continuously exposed to hazardous noise levels (Fig. 16-5). In the initial stages of development, the loss usually occurs at frequencies lying between 3,000 and 6,000 Hz. The maximum loss is usually centered at 4,000 Hz. The audiometric configuration, therefore, is characterized by a downward slope with greater loss in the high-frequency region (3,000–6,000 Hz) than in the low- and mid-frequency regions (250–2,000 Hz). As the NIHL accumulates following further exposure, the 4,000-Hz loss increases in magnitude and the adjacent (higher and lower) frequencies also become increasingly affected. The progressive nature of NIHL may eventually result in a moderate to severe impairment across most of the usable hearing frequency range (250-8000 Hz) unless preventive measures are taken to reduce the degree of hazard imposed by the noise.

Although the diagnosis of a permanent NIHL may be indicated by the audiometric configuration of the hearing loss (the 4,000-Hz notch), it would be premature to make a definitive diagnosis unless additional factors are considered, such as: (1) What is the duration, type, and time-weighted average of the individual's noise exposure? (2) What is the individual's hearing both before and after exposure? (3) What is the age and general health of the individual? (4) Are there any other disorders that may result in

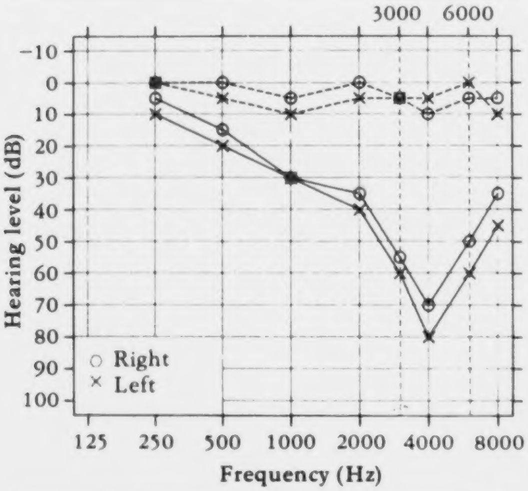

Fig. 16-5. An example of a typical audiogram from a normal individual (dashed lines) and an individual with a bilateral sensorineural hearing loss resulting from excessive noise exposure. Note the maximum loss at 4,000 Hz and the spread of loss to the lower frequencies.

hearing impairment (such as middle-ear disorders, congenital factors, Meniere's disease, an eighth cranial nerve lesion, ototoxicity, and presbycusis)? Consideration of these questions provides important information as to whether the cause and degree of impairment can be solely attributable to noise exposure. Two major diagnostic problems are distinguishing NIHL from hearing loss associated with presbycusis or ototoxic agents and determining the degree of impairment attributed to the aging process. A reported history of tinnitus or "muffled" hearing occurring immediately after any noise exposure or after leaving the work environment and a characteristic 4,000-Hz notch on the audiogram strongly suggest an occupational NIHL hearing loss. Complaints of vertigo are also common.

People usually do not report any difficulty in hearing until a hearing loss of more than 25 dB HL occurs at a frequency at or below 4,000 Hz. Difficulty in hearing the high-frequency sounds of speech (such as s, f, k, t, and sh) may provide the only clue to the individual of an NIHL. Performance on speech intelligibility tasks varies considerably depending on the magnitude of the loss and the affected frequencies. If the hearing loss is confined to frequencies above 3,000 Hz, speech intelligibility measured in quiet surroundings is usually within normal limits. As the frequencies below 3,000 Hz become involved, intelligibility decreases in relation to the degree of impairment. Given that approximately 95 percent of the frequency components in speech lie between 300 and 3,000 Hz, it should not be surprising to find a deterioration in speech intelligibility performance once the NIHL extends into this range of frequencies. Also, individuals with sensorineural hearing loss, due either to noise exposure or other factors, usually have greater difficulty understanding speech against a competing background noise environment than in a quiet environment. This common complaint may be minor if the hearing loss is restricted to frequencies at or above 3,000 Hz but may present market difficulty for those with losses below 3,000 Hz. Since the usual pattern of progressive NIHL is one in which the speech frequencies are affected last, it is important to identify NIHL during its initial stages to help prevent future deterioration of hearing sensitivity and speech discrimination abilities.

Occupational health nurses and physicians involved in assessing and monitoring hearing status in hearing conservation programs should refer the worker to an audiologist if a significant change in hearing level (≥ 10 dB at any frequency in either ear) is observed after the worker has had a minimum of 48 hours to recover from environmental noise exposure. Audiological management of the individual with NIHL may include the use of hearing aids, aural rehabilitation, and assistive listening devices to help improve some of the communication dysfunction experienced in certain listening situation. What, if any, strategies are implemented depends largely on the severity of the communication handicap produced by the noise exposure and the listening needs of the individual.

ATSDR
September 1993
Case Studies in Environmental Medicine

29

Reproductive and Developmental Hazards

Environmental ALERT . . .

- ☑ ***Approximately 8% of all couples are infertile.***
- ☑ ***It is estimated that 15% to 20% of all recognized pregnancies end in spontaneous abortions.***
- ☑ ***Of the 3 million infants born during the 1980s, approximately 7% were low birth weight, 5% were preterm, 2% to 3% had major congenital anomalies, and an unknown number have developmental or functional problems in childhood.***
- ☑ ***The extent to which environmental or occupational exposures affect these statistics is unknown.***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. See page 39 for more information about continuing medical education credits and continuing education units.

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

Case Study

From an article in your local newspaper, you learn that an underground waste solvent storage tank at a local semiconductor manufacturing plant is leaking toxic chemicals. According to the plant manager, the tank, which contains mostly 1,1,1-trichloroethane (TCA), is located about 2000 feet from a well that supplies drinking water to a nearby residential area. The article also mentions that at the time the leak was discovered, the concentration of TCA in the well was 1700 ppb. The well was immediately removed from service. The newspaper article states that as reporters interviewed residents for the story, they were told about five cases of spontaneous abortion and four cases of cardiac defects in the area.

Two weeks later, TCA levels in the well reached 8800 ppb, and minor amounts of 1,1-dichloroethylene (DCE) were found. Eighteen of your patients received water from the contaminated well, and several of them, including a 30-year-old pregnant patient, have requested consultations with you. After listening to their concerns, you contact the Agency for Toxic Substances and Disease Registry (ATSDR) to request assistance. In the health consultation provided, ATSDR concludes that the levels are far above levels established to protect public health; however, no human epidemiologic studies have been reported that adequately address reproductive effects caused by TCA or DCE. Data from animal studies do not suggest adverse reproductive or developmental outcomes from ingestion of these chemicals.

ATSDR decides to conduct a Public Health Assessment for this site. While collecting information for the health assessment, ATSDR finds that birth certificates for the county do not reveal an excess of adverse pregnancy outcomes in the water-service area compared with the rest of the county. However, because only 20% of all birth defects are typically reported on birth certificates, the agency advises that birth certificate studies alone cannot rule out an increase of birth defects; furthermore, vital records do not provide data on spontaneous abortions.

Currently, ATSDR is developing a protocol for an epidemiologic study to determine whether an association exists between exposure to the contaminated well water and congenital anomalies and spontaneous abortions. Pending the outcome of the epidemiologic study, you must communicate the risk of adverse reproductive and developmental effects due to toxic exposures. How will you address the following questions from your patient who is pregnant and her neighbors?

Pretest

(a) *Can adverse reproductive effects such as spontaneous abortion and birth defects be caused by drinking and using contaminated well water?*

(b) *I am 3 months pregnant. How will this exposure affect my pregnancy?*

(c) *Can I breast-feed if I have been drinking the contaminated water?*

(d) *My wife is having trouble getting pregnant; could this chemical exposure be responsible?*

(e) *We are planning to become pregnant; is it safe to do so?*

(f) *What is the health consultation provided by ATSDR? What is a public health assessment?*

Answers to the Pretest questions are on pages 13-16.

The Magnitude of the Problem

☐ **About one in twelve couples of reproductive age in the United States is infertile.**

☐ **At least 40% of all conceptions are lost before the 28th week of gestation.**

Several adverse reproductive effects can result from exposure of men and women to biologic, chemical, or physical hazards. Damage to the male or female germ cells can reduce fertility, and exposure before or during gestation can cause early pregnancy loss (clinically manifested as menstrual irregularity or infertility), spontaneous abortion, preterm or low-birth-weight neonates, birth defects, abnormal growth and development, and carcinogenesis (manifested as childhood cancer). Accurate data on reproductive and developmental effects are limited by the intrinsic difficulty of diagnosis and the lack of a national data collection system. Nevertheless, some estimates of adverse reproductive and developmental outcomes in the United States have been made.

About one in twelve couples of reproductive age in the United States is infertile. (A couple is deemed infertile if conception has not occurred after 1 year of unprotected sexual intercourse.) At least 40% of all conceptions are lost before the 28th week of gestation. About 2% to 3% of all newborns (approximately 3 million during the 1980s) have major congenital anomalies, 7% are low birth weight, 5% are preterm, and an undetermined number have developmental or functional problems in childhood. The causes of most of these adverse outcomes are unknown. If even a small percentage of these effects is attributable to environmental or occupational exposures, the number of families affected is large.

Chemical Agents and Adverse Outcomes

☐ **Many chemical agents are suspected of causing adverse reproductive or developmental effects; however, strong evidence exists for only a few.**

☐ **Folic acid supplements administered during the periconceptual period may prevent fetal CNS anomalies.**

To cause reproductive or developmental harm, toxicants must be absorbed into the bloodstream and pass from the blood to the reproductive organs or through the placenta to the fetus. Many chemical hazards react with the first tissues they contact—eyes, nose, throat, lungs, or skin—and rarely enter the bloodstream. Hence, these substances are unlikely to affect reproduction or fetal development. The following are examples of substances that are unlikely to enter the bloodstream in significant amounts, except when ingested.

ammonia
asbestos
chlorine
fiberglass
hydrochloric acid
nitric acid
potassium hydroxide
silica
sodium hydroxide
sodium hypochlorite (bleach)
sulfuric acid

Much of what we know about chemical exposures and their effects on reproduction and fetal development is from research using experimental animals. Effects of an absorbed toxicant may vary among the animal species and even among different strains of the same species. Extrapolating positive findings from animal studies to humans involves great uncertainty, and negative animal studies do not necessarily mean a compound poses no risk to humans. Differences in species response can be due to genetic variability, to differences in absorption and metabolism (including activation of the toxicant), or to different types of interactions within cells and tissues. Thalidomide, which has no detectable effect on mouse embryos but caused limb deformities in humans and higher primates, illustrates the variability of response among species.

Most human data are from exposures that occurred in the workplace, but in many cases, the data are inconclusive or difficult to interpret. Strong positive associations between a hazard and reproductive or developmental effects have been found for only a few substances including lead, mercury, certain organic chemicals (e.g., ethanol and ethylene oxide), and ionizing radiation. Certain biologic agents (e.g., rubella and mumps) are also strongly associated with adverse reproductive or developmental outcomes. Tobacco smoke has been reported to reduce fertility in both males and females.

Table 1 lists some environmental or occupational agents suspected to cause decreased female reproductive capacity or adverse developmental effects in the fetus. Some therapeutic agents reported to affect female reproductive capacity include steroids, alkylating agents, methotrexate, levodopa, quinacrine, appetite suppressants, opioids, antipsychotics (e.g., phenothiazines), antidepressants (e.g., imipramine, amitriptyline, and monoamine oxidase inhibitors), serotonin, sympathomimetic amines (e.g., epinephrine, norepinephrine, amphetamines), and reserpine.

Antifolate agents have been associated with macroscopic malformations in the fetus, especially central nervous system anomalies. Malformations have included spina bifida, hydrocephaly, anencephaly, and meningoencephalocele. To reduce the risk of having a pregnancy affected with neural tube defects (NTDs), the United States Public Health Service recommends that all women of reproductive age consume 0.4 milligrams (mg) of folic acid per day. Principal dietary sources of this vitamin include green, leafy vegetables, broccoli, spinach, mushrooms, liver, nuts, dried beans, peas, egg yolk, and whole-wheat bread. A varied diet that includes fresh vegetables and fruits generally provides enough folic acid for the body's needs. However, women who have had a prior NTD-affected pregnancy are at high risk of having a subsequent affected pregancy. In 1991, the Centers for Disease Control and Prevention (CDC) recommended that these high-risk women who are *planning* to become pregnant consult their physicians about taking 4.0 mg of folic acid per day during the periconceptual period (1 month before conception to 3 months after).

Table 1. Agents associated with adverse female reproductive capacity or developmental effects in human and animal studies*

Agent	Human Outcomes	Strength of Association in Humans†	Animal Outcomes	Strength of Association in Animals†
Anesthetic gases¶	Reduced fertility, spontaneous abortion	1,3	Birth defects	1,3
Arsenic	Spontaneous abortion, low birth weight	1	Birth defects, fetal loss	2
Benzo(a)pyrene	None	NA §	Birth defects	1
Cadmium	None	NA	Fetal loss, birth defects	2
Carbon disulfide	Menstrual disorders, spontaneous abortion	1	Birth defects	1
Carbon monoxide	Low birth weight, fetal death (high doses)	1	Birth defects neonatal mortality	2
Chlordecone	None	NA	Fetal loss	2,3
Chloroform	None	NA	Fetal loss	1
Chloroprene	None	NA	Birth defects	2,3
Ethylene glycol ethers	Spontaneous abortion	1	Birth defects	2
Ethylene oxide	Spontaneous abortion	1	Fetal loss	1
Formamides	None	NA	Fetal loss, birth defects	2
Inorganic mercury ¶	Menstrual disorders, spontaneous abortion	1	Fetal loss, birth defects	1
Lead¶	Spontaneous abortion, prematurity, neurologic dysfunction in child	2	Birth defects, fetal loss	2
Organic mercury	CNS malformation, cerebral palsy	2	Birth defects, fetal loss	2
Physical stress	Prematurity	2	None	NA
Polybrominated biphenyls (PBBs)	None	NA	Fetal loss	2
Polychlorinated biphenyls (PCBs)	Neonatal PCB syndrome (low birth weight, hyperpigmentation, eye abnormalities)	2	Low birth weight, fetal loss	2
Radiation, ionizing	Menstrual disorders, CNS defects, skeletal & eye anomalies, mental retardation, childhood cancer	2	Fetal loss, birth defects	2
Selenium	Spontaneous abortion	3	Low birth weight, birth defects	2
Tellurium	None	NA	Birth defects	2
2,4-Dichlorophenoxyacetic acid (2,4-D)	Skeletal defects	4	Birth defects	1
2,4,5-Trichlorophenoxyacetic acid (2,4,5-T)	Skeletal defects	4	Birth defects	1
Video display terminals	Spontaneous abortion	4	Birth defects	1
Vinyl chloride¶	CNS defects	1	Birth defects	1,4
Xylene	Menstrual disorders, fetal loss	1	Fetal loss, birth defects	1

* Major studies of the reproductive health effects of exposure to dioxin are currently in progress.

† 1 = limited positive data 3 = limited negative data
2 = strong positive data 4 = strong negative data

§ Not applicable because no adverse outcomes were observed

¶ Symbol used to designate agents that may have male-mediated effects

Toxicology of Reproductive Function

Germ Cell Development

Female. Oogonia develop in the female during fetal life when they undergo the first meiotic division. As a result, a woman is born with a full complement of oocytes. Through natural processes, the number of oocytes decreases from a maximum of about 7 million in the 5th gestational month to about 400,000 at puberty. Only 300 to 500 of the oocytes remaining at puberty will mature during a woman's reproductive life span.

The oocytes rest in the ovary until ovulation occurs, which for some oocytes may be 45 years or more after formation. At the start of the menstrual cycle, a group of small primary follicles begins to develop, each containing an oocyte. Release of pituitary follicle-stimulating hormone (FSH) supports the selection and growth of a dominant follicle; the remaining follicles degenerate. The growing follicle produces estrogen, which causes proliferation of endometrial tissue. When a critical blood concentration of estrogen is reached, the anterior pituitary releases a mid-cycle burst of hormones (FSH and luteinizing hormone [LH]), causing the follicle to rupture and ovulation to occur. The remaining cells of the ruptured follicle form the corpus luteum.

Fertilization can occur within 12 hours after ovulation. In the absence of fertilization, the corpus luteum degenerates. The consequent decrease in ovarian steroids produces ischemia and sloughing of the endometrium, resulting in menstruation. If fertilized, the ovum completes a second meiotic division, forming a zygote that undergoes several rapid cell divisions to become a blastocyst. The blastocyst implants in the endometrium approximately 5 days after fertilization.

Because many opportunities for exposures exist throughout a woman's life and there is no mechanism for reproductive regeneration, the potential for damage to the oocytes is significant. Researchers are elucidating the mechanisms by which oocyte damage or loss occurs; however, no studies have documented an association between exposure to industrial chemicals and oocyte damage or loss, which can cause infertility or premature menopause.

Male. In contrast to oocyte formation, spermatozoa are in continual production in stem cells after puberty. In humans, spermatozoa mature in an average cycle length of 74 days.

At precise intervals, primitive spermatogonia in the testes proceed from the basement membrane to the lumen of the seminiferous tubule where they undergo mitotic and meiotic cell divisions. Each germ cell duplicates itself (meiosis I), and each resulting diploid cell

☐ **Females are born with a full complement of oocytes. In contrast, spermatozoa are in continual development in males after puberty.**

☐ **Because reproductive regeneration does not occur in females, the ramifications of oocyte damage are significant.**

☐ **Chemical exposures to males can cause adverse pregnancy outcomes by several mechanisms.**

(46 chromosomes) divides into two haploid cells with 23 chromosomes each (meiosis II). Haploid cells then undergo spermiogenesis, developing a head, midpiece, and tail. The head consists of the sperm nucleus and the acrosome that contains the enzymes necessary for egg penetration.

After leaving the testes, sperm acquire motility and fertilizing capacity during transit through the epididymis and vas deferens. Sperm transport is dependent on the production of seminal fluid by the seminal vesicles. Sertoli cells in the testes play an important role in initiating spermatogenesis, synthesizing essential proteins, and providing nurturance. Supporting Leydig cells manufacture and secrete testosterone, which helps to maintain spermatogenesis and is essential for sexual interest and activity.

Exposure to ionizing radiation (alpha, beta, and gamma radiation; X rays), heat, or certain chemicals (Table 2) has been documented to cause male infertility and decreased libido. Destruction of the basic stem-cell spermatogonia usually causes permanent infertility; damage during subsequent stages of the maturation process is potentially reversible. Chemical exposure to the male can cause adverse pregnancy outcomes not only by damaging the sperm, which can produce an abnormal zygote, but possibly also by transmission of toxic agents in seminal fluid. In addition, contaminated skin and clothing of the male is a potential source of toxicant exposure to the pregnant woman.

Endocrine Function

☐ **Reproductive function in both men and women depends on the endocrine cycle, which is sensitive to physical and chemical agents.**

Reproductive function in men and women depends on the functioning of the neuroendocrine system. For men, FSH from the pituitary and testosterone from the Leydig cells of the testes act upon the Sertoli cells to initiate spermatogenesis. Pituitary LH induces high intratesticular concentrations of testosterone. For women, reproductive function requires pituitary LH and FSH, ovarian and adrenal estrogen, and progesterone.

Endocrine functioning in both men and women can be interrupted by agents with steroid-like activity or by neurologic effects induced by stress. Disorders of circadian rhythm, as can occur with some types of rotating work schedules, can also affect the endocrine cycle. The clinical results may be menstrual disorders in women and disorders of libido in both sexes.

Table 2. Exposures associated with male reproductive dysfunction

Agent	Human Outcomes	Strength of Association in Humans*	Animal Outcomes	Strength of Association in Animals*
Boron	Decreased sperm count	1	Testicular damage	2
Benzene	None	NA†	Decreased sperm motility, testicular damage	1
Benzo(a)pyrene	None	NA	Testicular damage	1
Cadmium	Reduced fertility	1	Testicular damage	2
Carbon disulfide	Decreased sperm count, decreased sperm motility	2,3	Testicular damage	1
Carbon monoxide	None	NA	Testicular damage	1
Carbon tetrachloride	None	NA	Testicular damage	1
Carbaryl	Abnormal sperm morphology	1	Testicular damage	1
Chlordecone	Decreased sperm count, decreased sperm motility	2	Testicular damage	2
Chloroprene	Decreased sperm motility, abnormal morphology, decreased libido	2	Testicular damage	1
Dibromochloropropane (DBCP)	Decreased sperm count, azoospermia, hormonal changes	2	Testicular damage	2
Dimethyl dichlorovinyl phosphate (DDVP)	None	NA	Decreased sperm count	2
Epichlorohydrin	None	NA	Testicular damage	2,3
Estrogens	Decreased sperm count	2	Decreased sperm count	2
Ethylene oxide	None	NA	Testicular damage	1
Ethylene dibromide (EDB)	Abnormal sperm motility	1	Testicular damage	2,3
Ethylene glycol ethers	Decreased sperm count	1	Testicular damage	2
Heat	Decreased sperm count	2	Decreased sperm count	2
Lead	Decreased sperm count	2	Testicular damage, decreased sperm count, decreased sperm motility, abnormal morphology	2
Manganese	Decreased libido, impotence	1	Testicular damage	1,3
Polybrominated biphenyls (PBBs)	None	NA	Testicular damage	1
Polychlorinated biphenyls (PCBs)	None	NA	Testicular damage	1
Radiation, ionizing	Decreased sperm count	2	Testicular damage	2

* 1 = limited positive data 3 = limited negative data.
2 = strong positive data 4 = strong negative data.

† Not applicable because no adverse outcomes were observed.

Developmental Biology

- **The major organ systems of the human embryo develop during the third to ninth week of gestation.**
- **It is uncertain whether a threshold exists for all teratogens.**

Soon after the blastocyst implants in the endometrium, trophoblastic cells rapidly proliferate, invading the uterine decidua and its vasculature. Placental circulation, which provides nutrient transport, is established by about the 17th day after ovulation. Substances that are of low molecular weight, lipophilic, and nonionized at physiologic pH readily diffuse across the placenta. The embryonic stage of development begins about the third week after ovulation. During the ensuing six weeks, the major organ systems of the embryo (i.e., cardiovascular, central nervous system, genitourinary, respiratory, endocrine, and immune system) form in a precisely timed sequence. Dramatic growth and maturation then continues during the remaining fetal period, until birth, when the average fetus weighs about 3000 to 3600 grams (about 6.6 to 8.0 pounds).

Exposures during weeks 1 and 2 after conception (i.e., the period of rapid division of the zygote, implantation, and formation of the bilaminar embryo) may cause early pregnancy loss by interfering with tubal transport or implantation. Heavy metals such as lead or copper have been found to inhibit implantation in experimental animals by interfering with uterine hormone-binding mechanisms.

Teratogenic effects usually occur during the critical periods of organogenesis. Different agents given at the same critical period can cause the same anomaly, and the same agent administered at different periods of organogenesis may cause different anomalies. An insult delivered just before or during the early stages of the development of a particular organ is most likely to render the organ abnormal. (See Table 3 for a list of agents and conditions that are teratogenic in humans.) Thalidomide taken by humans between the 27th and 29th day of pregnancy caused limb deformities.

Table 3. Known or suspected human teratogens

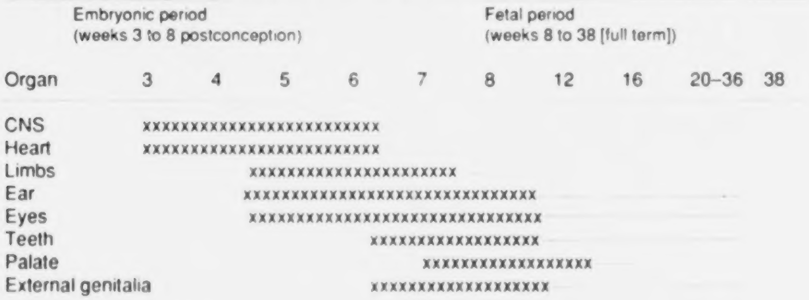
Chemicals/Drugs
- Aminopterin
- Androgenic hormones
- Antithyroid drugs
- Busulfan
- Chlorobiphenyls
- Coumarin anticoagulants
- Cyclophosphamide
- Diethylstilbestrol
- Diphenylhydantoin
- Lithium
- Mercury, organic
- Methimazole
- 13-cis-Retinoic acid
- Tetracyclines
- Trimethadione

Radiation
- Atomic weapons
- Radioiodine
- Radiotherapy

Infectious agents
- Cytomegalovirus
- Hepatitis B virus
- Herpes simplex virus
- Rubella virus
- Treponema pallidum (syphilis)
- Toxoplasma gondii
- Varicella virus (chicken pox)
- Venezuelan equine encephalitis virus

Thus, the timing of an exposure often determines its effect. In the first 2 weeks after conception, when organogenesis has not yet begun, the most probable effect of significant exposure is severe damage and death of the embryo; that is, immediate postconception exposures do not usually result in specific birth defects. The period from 3 to 9 weeks postconception is a critical time when classic birth defects can be induced (Figure 1). Growth deficits, minor morphologic abnormalities, and postnatal functional abnormalities typically occur after 9 weeks of gestation. Carcinogens potentially can exert an effect at any stage in development.

Figure 1. Periods of sensitivity* for major organ systems



* period of high sensitivity = xxxxxx; period of less sensitivity =

Adapted from Hays DP, Pagliaro LA. Human teratogens. In: Pagliaro LA, Pagliaro AM, eds. Problems in pediatric drug therapy. Hamilton, IL: Drug Intelligence Publications, 1987.

Some chemical toxicants cause severe effects on the embryo and have no effect on the pregnant woman; others affect the embryo only at maternally toxic doses. Traditional theory contends that a threshold exists for defects of organogenesis because the embryo can usually repair damage caused by low levels of exposure. Exposure must occur above the threshold to cause damage. However, recent studies of the fetal metabolism of xenobiotics suggest that a threshold may not exist for all substances; for example, no threshold has been defined for carcinogens.

A toxic agent may affect the embryo even when exposure occurred to the mother or father before conception. In some cases, damage to genetic material in the ovary or sperm (mutagenesis) results in pregnancy loss or inheritable defects in offspring. In other cases, exposure before conception affects the development of the fetus because the toxicant persists in the maternal body. For example, polychlorinated biphenyl (PCB) compounds are stored in adipose tissue for a significant period of time, and lead may be stored in bone for years. Toxicants generally reach a steady state between the storage depot and the blood, but the stresses of pregnancy may cause the toxicant level in the bloodstream to increase. The fetus may be exposed to these body stores through maternal circulation.

Toxicants can also be passed to the infant through breast feeding. Transfer of chemicals into breast milk occurs primarily by passive diffusion. Table 4 lists the milk-to-maternal plasma ratios for several toxicants; substances with ratios greater than one tend to be highly lipophilic and nonpolar molecules. High maternal exposures, such as those caused by the ingestion of PCB-contaminated rice oil in Japan in 1968, have led to disease in infants, either through exposure in utero or through breast feeding. Chemical exposures by routes other than maternal ingestion have not been reported to produce adverse health effects in breast-fed infants.

Table 4. Milk-to-maternal plasma ratios in exposed women

Chemical	Milk/Plasma Ratio
Mercury, inorganic and organic	0.9
Lead	≤ 1.0
Tetrachloroethylene	3.0
Polybrominated biphenyls (PBBs)	3.0
Polychlorinated biphenyls (PCBs)	4.0–10.0
Dieldrin	6.0
o,p-Dichlorodiphenyltrichloroethane (DDT) residues	6.0–7.0

Adapted from Wolff MS. Occupationally derived chemicals in breast milk. Am J Ind Med 1983;4:259-281.

Management

Male infertility secondary to occupational exposure may be reversible because of the capacity of the male to regenerate sperm. In men chronically exposed to 1,2-dibromo-3-chloropropane (DBCP), recovery occurred in those with oligospermia (a subnormal concentration of spermatozoa in the semen), although it required as long as 18 months in some cases. However, in men exposed to doses of DBCP that caused azoospermia (absence of living spermatozoa in the semen), long-term sterility resulted. In addition to changes in sperm counts in DBCP-exposed workers, testicular biopsy revealed atrophy of the seminiferous epithelium or tubular hyalinization with few germ cells, and in some tubules only Sertoli cells persisted. These histopathologic changes were associated with elevated LH and FSH plasma levels and decreased testosterone levels. Follow-up studies of DBCP-exposed workers showed recovery was directly linked to FSH levels (i.e., greater recovery occurred in men whose FSH levels were normal). Data from patients treated with high-dose therapeutic radiation suggest that even azoospermia can be reversed in some cases, but recovery may take 4 to 5 years. (Acute exposure to lower doses of radiation [~15 rads] affects spermatogenesis only transiently.)

☐ **Infertility secondary to chemical exposure may be reversible in males because of continuous sperm production.**

☐ **The effects of chemical exposures on female fertility are unknown in most cases.**

Volume, standardized count, motility, and morphology analysis should be performed on two semen samples to make a diagnosis of male infertility. Normal values for semen analysis are listed in Table 5. No clear guidelines are available on how much of a change in semen parameters constitutes significant improvement. Although 20 million sperm per milliliter (mL) of semen is traditionally accepted as a minimal sperm count, conception can occur with counts below this value, and some men who have higher counts may still be infertile. An improvement in the sperm count from 5 million to 40 million per mL is clinically significant, but a change from 10 million to 15 million per mL is probably not. Consultation with a fertility expert may be helpful.

Table 5. Normal values for semen analysis

Volume	2–6 mL
Sperm concentration	20–250 (10^6/mL)
Sperm motility	> 50 %
Sperm vitality	≥ 50 %
Normal forms	≥ 60 %

If abnormal values for semen analyses are found, and no other cause for the abnormalities is obvious, exposures should be eliminated using engineering controls and protective equipment, changing the patient's job, or substituting less toxic materials. If removal from exposure is used as a diagnostic test, removal should continue as long as 18 months before the trial is concluded. (Semen analyses should be performed every 2 to 3 months to monitor improvement in sperm parameters.) If biomarkers are available to monitor body burden of a toxicant, as with lead, the 18-month period should be measured from the time the biomarker indicates that the body burden of the toxicant has returned to the normal range.

Even if a trial involving removal from exposure has been undertaken, it is important to remember that infertility may be a problem of the couple, rather than due solely to the man or the woman. For example, a submaximal sperm count in association with abnormalities of cervical mucus can lead to infertility, when neither condition alone would prevent conception. If the fertility evaluation suggests that infertility is due to a cumulative effect of the couple and the man is exposed to an identified toxicant, a trial of removal from exposure may still be appropriate while measures to correct the other disorders are carried out.

Occasionally, male infertility is due to both a medical condition and an identifiable occupational or environmental cause. The therapeutic approach in these cases should be one that recognizes both aspects of the problem. For example, if a varicocele (a condition manifested by abnormal dilation of the veins of the spermatic cord, which is a frequent cause of oligospermia) coexists with exposure to lead, elimination of the lead exposure could be tried along with consideration of corrective surgery.

Chemical exposures associated with infertility have thus far been linked primarily to effects on the male. Potentially comparable effects on females have not been elucidated because parameters that affect female reproductive capacity cannot be easily measured. Chemical exposures should be strictly controlled or eliminated for all females of reproductive age. At the very least, pregnant females who have had exposures to organic solvents or lead should receive ultrasound monitoring and cervical checks if they have engaged in strenuous work and are at risk for preterm delivery.

Regulation of Reproductive Hazards

☐ **Regulatory standards may not be protective of reproductive health.**

The most direct approach to reducing environmental or work-related adverse reproductive outcomes is by controlling contamination in the environment and by limiting exposure to toxic substances in the workplace. Various statutes regulate exposure to reproductive toxicants encountered in the workplace, and a variety of regulatory agencies are responsible for enforcing these statutes. No single agency has complete regulatory responsibility for reproductive and developmental toxicants.

The most comprehensive federal statute governing health and safety in the workplace is the Occupational Safety and Health Act of 1970. The Occupational Safety and Health Administration (OSHA) is empowered to promulgate permissible exposure limits (PELs) for toxic substances in the workplace, including those posing risks to the reproductive health of workers. However, only a handful of the thousands of chemicals currently in use are regulated because of their potential to produce adverse reproductive effects. Many substances that threaten to damage reproduction may do so at exposure durations or levels lower than the PELs set to protect against other effects.

The Toxic Substances Control Act (TSCA) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) mandate EPA to require the testing of products for toxicity and to limit the commercial use of toxic substances in the environment and workplace. Regulation of a substance under TSCA or FIFRA could theoretically result in a ban of the product. Reproductive toxicity, however, has seldom been the major consideration in the decision to ban a substance.

Answering the Questions

Clinicians are frequently questioned about potential risks to the reproductive health of men and women exposed to chemical toxicants and about the causes of adverse pregnancy outcomes. These questions most often come from persons exposed in the workplace; however, many communities have hazardous substances in air, water, and soil. The number of people potentially affected by environmental exposures is relatively large, and these persons are probably more susceptible to toxicants than healthy workers. Yet, most references on the medical evaluation of adverse pregnancy outcomes or infertility fail to mention the role of environmental toxic exposures.

Clinicians have been given little guidance in answering patients' questions concerning adverse reproductive and developmental outcomes. Most of the information available is from animal studies, and no consensus exists on extrapolating from experimental animal data to human risk. Nevertheless, much can be done with the information published; reasonable and informed decisions can be made.

The most commonly asked questions regarding the reproductive and developmental effects of exposures are the questions in the Pretest on page 1. These questions are answered below in the context of exposure to TCA and DCE, as presented in the case study, but additional information is given regarding exposures to other substances as well.

a) "Can adverse reproductive effects such as spontaneous abortion and birth defects be caused by drinking and using contaminated water?"

It is unlikely that the adverse reproductive and developmental effects stated in the case study were caused by exposure to TCA or DCE, either by drinking or using contaminated water or by exposures to these substances at work. In general, if a link between an adverse reproductive outcome and an environmental exposure is strongly suspected and the exposure can be stopped, the parents can be reassured that future pregnancies will not be at increased risk. If no clear cause is obvious, but exposure to a potential toxicant exists, the management of future pregnancies becomes a concern.

Etiologic questions may be extremely difficult to answer in a legal context. Typically, data are insufficient to link specific exposures to specific outcomes. Nevertheless, the same rules used to evaluate any suspected environmentally or occupationally caused diseases apply. Other known causes of the abnormality must be excluded and the nature, timing, and degree of exposure must be estimated to determine whether the dose is comparable to the dose associated with the particular adverse effect.

Parents who have suffered adverse reproductive or developmental outcomes require sensitive counseling because they may be concerned about the child's health, their own health, the presence of undetected genetic problems, and risks in future pregnancies. An environmental and occupational history should be obtained, and evaluation should proceed as medically indicated. (See *Case Studies in Environmental Medicine: Taking an Exposure History*, ATSDR, 1993.)

b) "I am 3 months pregnant; how will this exposure affect my pregnancy?"

Many substances have been linked to increased rates of spontaneous abortion. TCA and DCE are not among these chemicals. If the literature or other sources reveal that an exposure has been associated with an increased risk of a birth defect, you can discuss this with the patient in the context of the timing of the exposure and background rates of adverse pregnancy outcomes in general. For example, the overall rate of a particular severe defect (without exposure) is 1 in 200 births. If a chemical exposure raises the risk of a *specific* defect from 1 in 2000 births to 3 in 2000 births (or 0.3 in 200 births), it would have a relative risk of 3 for that defect. The overall risk of the defect is then increased from 1 per 200 (without exposure) to 1.3 per 200 (with exposure). For many people, understanding this relative risk may be reassuring. An increased risk of early fetal loss or of giving birth to a small-for-age baby is not an indication for therapeutic abortion.

However, for some exposures, the risk of adverse outcomes may be considerable. In cases in which the risk is high, some persons may choose to terminate the pregnancy. For example, acute exposure to ionizing radiation of greater that 30 rads at any stage of gestation is associated with a high probability of congenital abnormalities. Another situation in which the relative risk is high is an acute poisoning (e.g., carbon monoxide poisoning) that results in severe anoxia of the mother, which can have severe consequences for the fetus.

Ultimately, the decision to maintain or terminate a pregnancy rests with the patient. What is considered a significant risk that warrants pregnancy termination depends on a complex set of patient values—individual, cultural, and social. It is the responsibility of health professionals to ensure that the patient's decision is as well informed as possible, in terms of both the risks and alternatives. When the relative risks are high, you may wish to refer your patient to a genetic counsellor for more help in making this decision.

c) "Is there danger to breast feeding if I have been drinking contaminated water?"

After the child is born, its growth and development can be affected by exposure to substances brought home on the clothes of family members or used in the home, and those excreted in breast milk. Obstetricians and pediatricians justifiably encourage breast feeding, which provides IgA, amino acids, and fats that are essential for the developing infant, and considerable psychologic advantages to both mother and child. Only in rare cases are the advantages of breast feeding outweighed by the transmission of toxic chemicals.

The dose of the chemical to which a breast-feeding infant is exposed depends on the biologic fate of the substance in the mother. Toxicants that are fat soluble may reach high levels in the breast milk, which may be the major route of excretion, even though maternal exposure has stopped. By contrast, many organic solvents, although fat soluble, are also excreted through the lung, liver, and kidneys, generally decreasing maternal body burden soon after exposure has stopped.

The acute health effects resulting from a given infant dose of a substance transmitted in breast milk have been defined for only a few substances. Furthermore, chronic effects of low-dose exposures are virtually unknown. These uncertainties make the decision of whether to breast feed a difficult one. The following guidelines for mercury, PCBs, organic solvents, and lead are based on the limited data available, the considerations outlined above, and the availability of a safe alternative.

1. Mercury is the only chemical for which an unequivocal guideline has been set in milk. U.S. Food and Drug Administration (FDA) guidelines set a maximum allowable concentration of mercury in over-the-counter milk at less than 4 micrograms per liter (μg/L).

2. Acute effects of PCBs or related halogenated hydrocarbons on the breast-feeding infant are unlikely at any maternal blood level. Unless the mother has ingested or otherwise has received a considerable dose, breast feeding can be continued in most cases.

3. Maternal exposure to organic solvents should be minimized during breast feeding. Because most organic solvents (including TCA) are excreted relatively rapidly, breast feeding can be resumed several days after an acute maternal exposure. In the interim, milk can be pumped from the breasts (to maintain lactation) and be discarded.

4. The Centers for Disease Control and Prevention (CDC) has set a current action level for blood lead in children of 10 μg/deciliter (dL); above this level, adverse health effects have been reported to occur in children. A woman who has been exposed to lead should consult her physician and have a determination of her blood lead level before breast feeding. (The ratio of the lead concentration in maternal blood (or plasma) to the concentration in maternal milk is approximately 1 [Table 4, page 10].)

d) "My wife is having trouble getting pregnant; could a chemical exposure that I am receiving be responsible?"

A couple is defined as infertile when conception has not been achieved after 1 year of unprotected sexual intercourse. Approximately 10% of all couples are infertile. Male factors are estimated to account for about 40% of this infertility, failure of ovulation for 10% to 15%, tubal factors for up to 30%, and cervical factors for about 5%. In approximately 10% to 20% of infertility cases, the cause is not identified.

Infertility associated with chemical exposures has thus far been linked primarily to effects on the male. This may be partially because semen can be measured and analyzed and thus provides a ready means of assessing reproductive health in men exposed to potential toxicants. No similar parameter is available to determine female reproductive health after chemical exposure. Changes in menstrual patterns may be a biomarker for chemically induced oocyte toxicity and are currently being investigated.

To demonstrate that male infertility is caused by a chemical exposure, the following four criteria must be met:

1. The results of at least two semen analyses must be abnormal (e.g., sperm must be inadequate in number or have abnormal morphology, poor motility, or decreased ability to penetrate the egg).

2. Other causes of infertility must be excluded. An abnormal semen analysis does not necessarily implicate a toxicant as a causative agent. Major causes of male infertility are primary endocrinopathy, prior testicular injury, testicular surgery, mumps, gonadotoxic drugs (e.g., chemotherapy with cytotoxic drugs or estrogens), varicocele, urologic abnormalities (e.g., retrograde ejaculation), ductal obstruction, venereal disease, or vasectomy. These may not cause infertility in all men who are affected by them.

3. Exposure to a toxicant known or suspected of causing infertility must have occurred. Table 2, page 7, lists substances that are known or suspected to cause male infertility in humans or have positive study results in experimental animals. Many agents have not been adequately studied, so clinicians should keep an open mind if the first two criteria have been met and if exposure involves an agent that chemically or structurally resembles an identified reproductive toxicant.

4. Because effects on spermatogenesis are usually reversible, a fourth diagnostic criterion is improvement after removal from exposure. A clear improvement after exposure ceases is compelling diagnostic evidence and may be especially helpful when data about the toxicant in question are limited. However, failure to improve does not demonstrate conclusively that exposure is not the cause because some toxicants affect the spermatogonial stem cells causing long-term or permanent infertility.

e) "We are planning to become pregnant; is it safe to do so?"

Answering this question for patients entails the following three steps:

- Reviewing the information on the exposure (e.g., agent, timing, dose)
- Reviewing the known effects of the exposure and the doses at which effects have been reported to occur
- Applying clinical judgment, taking the individual patient into account

Although current data do not permit a rigid or scientific consensus on guidelines, the following general paradigm is proposed:

1. If the exposure occurs in the home or community environment setting and it is demonstrated that the patient is exposed at doses that cause significant risk, immediate exposure reduction, perhaps even relocation, is required. If the exposure occurs in the occupational setting, decreasing exposure through engineering controls, materials substitution, or job transfer is recommended.
2. Rigorous control of exposure is necessary if significant risk is suspected. (A combination of experimental animal and human data is used to determine if a risk is suspected.)
3. If only minimal exposure to established or suspected agents occurs, simple modifications of the home, community, or workplace environments to reduce or eliminate contact may be feasible.

Suggesting a job transfer can raise difficult social and economic issues. Some employers have a policy regarding transfer during pregnancy, and many will follow the recommendation of a physician regarding job relocation. However, an employer usually is not required to transfer a pregnant worker to a safe job (see *Suggested Reading List*, page 17).

The difference in emphasis between the answers to this question and (b) above is important. The answer to (b) considers medical treatment that has potential morbidity and mortality implications for the patient, whereas this answer affords the opportunity to practice prevention. Preventive actions are more desirable and often require less certainty than other interventions.

f) "What is an ATSDR health consultation? What is an ATSDR public health assessment?"

A health consultation is ATSDR's response to a question or request for information pertaining to a hazardous substance or site. The procedure provides advice on specific public health issues that arise from actual or potential exposure to a hazardous substance. When a rapid response is required, a health consultation is a more limited method of addressing concern about potential adverse health effects than is an ATSDR public health assessment.

A public health assessment is a formal evaluation of relevant environmental data, health outcome data, and community concerns associated with a site where a hazardous substance has been released. In the process of assessing the current or future impact of a release on public health, studies or actions needed to evaluate, mitigate, or prevent human health effects are defined. Written health advisories or other recommendations may be developed and issued.

897

Suggested Reading List

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Government Publications

American College of Obstetricians and Gynecologists. Guidelines on pregnancy and work. DHEW (NIOSH) Publication No. 78-118, 1977.

Centers for Disease Control and Prevention. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. MMWR 1992;41:1-7.

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Other Sources of Information

Many of the issues in the series *Case Studies in Environmental Medicine* concern individual chemicals; each contains information on the reproductive and developmental effects of that chemical. Members of the Organization of Teratology Information Services (OTIS) and of the Association of Occupational and Environmental Clinics (AOEC) are listed by state in Appendices I and II, respectively.

In addition, risklines (telephone hotlines) or clinics that address reproductive and developmental hazards are available in the United States and Canada. Many of the following organizational resources are listed in *Reproductive Hazards in the Workplace: A Syllabus for Cinicians*, by M. Paul and S. Kurtz, University of Massachusetts, 1990.

Arizona

Arizona Teratogen Information Service. Arizona Health Sciences Center, Tucson, AZ. Serves Arizona only: (602) 626-6016 or (800) 362-0101 (Arizona only)

California

Hazards Evaluation System and Information Service (HESIS), California Department of Health Services, Berkeley, CA. Serves California only: (510) 540-3014 (collect calls accepted from within California)

Connecticut

Connecticut Pregnancy Exposure Riskline, University of Connecticut Health Center, Farmington, CT. Serves Connecticut only: (203) 674-1465 or (800) 325-5391 (Connecticut only)

Colorado, Montana, Nevada, and Wyoming

Rocky Mountain Poison and Drug Center and the University of Colorado Genetics Unit, Denver, CO. Serves primarily Colorado, Montana, Nevada, and Wyoming: (800) 332-3073 (Colorado only), (800) 525-5042 (Montana only), (800) 446-6179 (Nevada only), (800) 442-2702 (Wyoming only). Out of state: (303) 629-1123; physicians only: (303) 270-8742

Florida

Teratogen Information Service, University of Florida, Gainsville, FL. Serves Florida only: (904) 392-4104

Illinois

Illinois Teratogen Information Service, Illinois Department of Public Health, Chicago, IL. Serves Illinois only: (312) 903-7441 or (800) 252-4847

Massachusetts

Occupational and Environmental Reproductive Hazards Center, University of Massachusetts Medical Center, Worcester, MA. Provides clinical consultation and health provider education regarding reproductive azards: (508) 856-6162.

Teratogen Information Service, Franciscan Children's Hospital, Boston, MA. Serves primarily Massachusetts but will accept calls from practitioners nationwide: (617) 787-4957 or (800) 322-5014 (Massachusetts only)

Nebraska

Nebraska Teratogen Project, University of Nebraska Medical Center, Omaha, NB. Serves primarily Nebraska but will accept calls from practitioners in surrounding states: (402) 266-2900

New Jersey

Teratogen Information Network, University of Medicine and Dentistry of New Jersey. Serves primarily New Jersey: (609) 757-7812 or (800) 441-0025 (New Jersey only)

Pennsylvania

Pregnancy Healthline, Pennsylvania Hospital, Philadelphia, PA. Serves primarily Pennsylvania: (215) 829-KIDS (829-5437)

Utah

Pregnancy Riskline, Utah Department of Health and University of Utah, Salt Lake City, UT. Serves Montana, Nevada, and Utah: (800) 521-2229 (Montana and Nevada only), (801) 583-2229 or (800) 822-2229 (Utah only)

Vermont

Vermont Pregnancy Risk Information Service, University of Vermont, Burlington, VT. Serves Vermont only: (802) 658-4310 or (800) 531-9800 (Vermont only)

Washington

Seattle Poison Center, Children's Hospital and Medical Center, Seattle, WA. Serves Washington only: (206) 526-2121 or (800) 732-6985 (Washington only)

Canada

A team of physicians and information specialists in the MotherRisk Program at the Hospital for Sick Children, Toronto, Ontario, ([416] 813-6780) will counsel a caller about the safety of an exposure to drugs, chemicals, or radiation during pregnancy or breast feeding. Please be prepared to provide them with the specific name of the product about which you are concerned and the exact dates of the exposure. They will not suggest or prescribe medication by telephone and will not answer questions about advanced maternal age, amniocentesis, chorionic villae sampling, or other pregnancy-related tests. Questions concerning a genetic condition should be directed to the Department of Clinical Genetics at the Hospital for Sick Children ([416] 813-6390).

Computer Databases

Computer databases dedicated to reproductive and developmental hazards

REPROTOX
Contact: Greta Ober
Reproductive Toxicology Center
Columbia Hospital for Women Medical Center
2425 L Street, NW
Washington, DC 20037
(202) 293-5137

TERIS
Contact: Janine E. Polifka, Ph.D.
Teratogen Information System (includes *Shepard's Catalog of Teratogenic Agents*)
Department of Pediatrics, TRIS WJ-10
University of Washington
Seattle, WA 98195

REPRORISK
Contact: Betty Dabney, Ph.D.
Micromedex, Inc.
600 Grant Street
Denver, CO 80203-3527
(303) 831-1400

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Childhood Asthma and Indoor Environmental Risk Factors

Claire Infante-Rivard

In a case-control study carried out in Montréal, Québec, Canada, between 1988 and 1990, indoor environmental factors were studied in relation to the incidence of asthma among 3- and 4-year-old children. Cases ($n = 457$), whose parents were recruited at a hospital emergency room, were children who had a first-time diagnosis of asthma (*International Classification of Diseases*, Ninth Revision, code 493) made by a pediatrician. Controls ($n = 457$) were chosen from family allowance files and were matched with case children on age and census tract. A telephone interview was administered to the children's parents. A 20% feasibility subsample was chosen to wear a nitrogen dioxide monitoring badge during a 24-hour period. Multiple conditional logistic regression analysis showed that after personal susceptibility factors were controlled for, the following were independent risk factors for asthma: the mother's heavy smoking (odds ratio (OR) = 2.77, 95% confidence interval (CI) 1.35–5.66), use of a humidifier in the child's room (OR = 1.89, 95% CI 1.30–2.74), and the presence of an electric heating system in the home (OR = 2.27, 95% CI 1.42–3.65). The presence of other smokers in the home was not quite significant (OR = 1.82, 95% CI 0.98–3.38). A history of pneumonia, the absence of breast feeding, and a family history of asthma were also significant risk factors. In a separate unmatched multivariate analysis of subjects who had worn the nitrogen dioxide badge, there was a dose-response relation between nitrogen dioxide (in parts per billion) and asthma. These results confirm the role of susceptibility factors in asthma and show that indoor environmental factors contribute to the incidence of asthma. *Am J Epidemiol* 1993;137:834–44.

air pollutants; asthma; child; environment; household articles; nitrogen dioxide; tobacco smoke pollution

Concern has arisen in recent years about indoor air pollution as a risk factor for asthma (1). Pollutants in the home are numerous, and their sources, such as tobacco smoking, are encountered frequently. Moreover, the energy crisis of the 1970s provoked changes in the way houses are insulated and built; one consequence is that air exchange rates in energy-efficient "tight" and "supertight" homes are substantially reduced in comparison with those in older conventional homes. Finally, it is recognized that most people spend 75–90 percent of their time indoors (2), a proportion that is likely to be greater in small children.

Indoor environmental factors that have received the most attention in the past are tobacco smoke and directly or indirectly measured nitrogen dioxide, mainly from gas appliances. The present study considered

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Abbreviations: CI, confidence interval; OR, odds ratio; ppb, parts per billion.

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these and other, less frequently studied potential risk factors for their relation to the incidence of asthma among 3- and 4-year-old children. The objective of the study was to estimate the contribution to asthma incidence of chemical, physical, and biologic indoor environmental factors, as well as family history of asthma and past infections, after accounting for personal susceptibility. A case-control study was carried out to meet this objective.

MATERIALS AND METHODS

Case ascertainment

Cases were 3- and 4-year-old children with a first-time diagnosis of asthma made by a pediatrician. We chose this age group to avoid the problem of differential diagnoses for asthma which is more likely at younger ages, and to allow for a plausible but reasonably short time period for risk factor assessment. Cases were recruited between January 1988 and December 1990 at the emergency room of Hôpital Sainte-Justine, the larger of two university-affiliated pediatric centers in Montreal, Quebec, Canada. A computerized roster is kept in the hospital's emergency room which includes the age of the child, the discharge diagnosis, and the child's medical record number. From this roster, 3- and 4-year-old children with a diagnosis compatible with any of those listed under *International Classification of Diseases*, Ninth Revision, code 493 had their hospital medical records checked for previous attendance with a similar diagnosis. Known (previously diagnosed) cases were rejected. A second screening for eligibility took place when the parents were asked whether the child had ever been diagnosed by a physician as having asthma. An additional criterion for eligibility was that the child reside in the greater Montreal region.

Control ascertainment

Controls were children of the same age (± 1 month) and the same census tract (in the urban area) or postal code (in the rural area) as the case at the time of diagnosis. A census tract is defined in the *Canadian Census Dictionary* (3) as a small geostatistical unit including a mean of about 4,000 persons with maximum economic and social homogeneity. In rural areas surrounding the city, a postal code area indicates a region served by the post office or the postal branch. Controls were chosen from computerized family allowance files for the target region. The family allowance is a government stipend awarded to all families with children. Eligibility for the family allowance program is based on the following: a child must be less than 18 years of age and must reside in Canada. In addition, at least one parent must be a Canadian citizen, a person admitted to Canada as a permanent resident according to the terms of the law, or a person who has been admitted to the country as a visitor or who is holding a visiting permit for at least 1 year, and whose revenue is taxable (4). For reasons of cost, the latest available files from 1987 were used during 1988 and most of 1989. The 1989 files were used until the end of the study in 1990. All children who were eligible on the basis of age and census tract or postal code were enumerated from 1 to *n*. To choose the first control, we randomly generated a number between 1 and *n*. If, based on a search of readily accessible sources of information on addresses and telephone numbers, this control was not available, the procedure was repeated.

Data collection

The list of potentially eligible cases and controls was given to a first interviewer, who contacted the parents to confirm that the case was one with a first-time diagnosis by a physician and that the control had had no previous diagnosis of asthma made by a physician. If the parents were willing to participate, an appointment for the interview was made. A telephone interview was conducted by a second interviewer who was blind to the case/control status of the child. The interview had to take place for both cases and controls within 1 month of the case child's visit to the emergency room.

The questionnaire measured potential risk factors in yearly periods from birth to the time of diagnosis. These factors were grouped into three categories. The first category was personal susceptibility factors, family history of asthma, and past infectious diseases: the child's allergies, e.g., to food or clothing; parental and sibling asthma; and history of eczema, pneumonia, and tonsillectomy. The second category, environmental exposures in the home of a chemical nature, included maternal and paternal smoking; other smokers in the home; exposure to gas cooking appliances, kerosene space heaters, insulation material, and a fireplace or wood stove; and year of home construction. Other environmental factors of a physical nature were type of home heating system; whether the house contained a central humidifier, air purifier, or air conditioning; and whether a humidifier was used in the child's room. Other biologic factors assessed included family pets, wall-to-wall carpeting, the amount of dampness on the windows, and occupant density per room.

In addition, during the winter months, mostly the winter of the last study year, a subsample of 20 percent of study parents were asked to have their children wear a passive nitrogen dioxide monitoring badge (5) for 24 hours as part of a feasibility study. The main sources of emission of nitrogen dioxide in the home are gas stoves, gas- and kerosene-fueled space heaters, and, to a lesser extent, tobacco smoking (6). According to our instructions, the badge could either be worn by the child when he or she was awake and playing or left in the room while the child was sleeping. All consecutively interviewed parents during that study period were asked to use the badge, regardless of the child's case/control status.

Nitrogen dioxide from the filter badge was analyzed spectrophotometrically in parts per billion (ppb). The sensitivity of the badge was 66 ppb per hour, and in one study it was reported to have a precision of 5.9 percent (mean percentage difference, in ppb, between replicate measures; standard deviation, 5.4 percent) (7). The child's case/control status was unknown to the laboratory personnel who conducted the tests. The nitrogen dioxide results, in ppb, were categorized as follows: <0.5, 0.5–10, >10–15, and >15.

The third category included information on other personal and social factors such as the sex of the child, mother's and father's educational level (elementary school, high school or equivalent, college or equivalent, and postgraduate schooling), and breast feeding.

Some of the environmental exposures, such as type of heating and the presence of cooking appliances, wood stoves, fireplaces, central air conditioning, and central humidifiers, were also ascertained for any day-care center attended by the child, where applicable.

Statistical analysis

Conditional logistic regression (8) was used to analyze the matched data sets (EGRET package; Statistics and Epidemiology Research Corporation, Seattle, Washington). Odds ratios and their 95 percent confidence intervals were estimated. All statistical tests were two-sided. All variables were defined as categorical indicators. Categories were defined a priori. The independent contribution of each variable was assessed after controlling for personal susceptibility factors such as history of allergies and eczema. A multivarite model was developed that included all variables except those relating to insulation materials and the year of construction of the first home inhabited by the child, since parents often could not provide information on these factors. Nitrogen dioxide was not included either, because only 140 subjects had their child wear the badge as instructed. However, using the 140 subjects with nitrogen dioxide measurements, an unconditional logistic regression analysis was conducted that included nitrogen dioxide and all of the variables that made an independent contribution in the conditional multivariate model.

Response

There were 631 confirmed eligible case children; parents of 627 were successfully interviewed, and four families refused to participate. However, 457 cases were used in the analysis because the controls for 170 of the cases could not be interviewed within 1 month of case ascertainment. This was mostly due to a delay in receiving and difficulty reading the computer tapes of the family allowance files at the beginning of the study and during the study's second year. Cases not included in the analysis were similar to those included with respect to age and sex distribution, the proportion with past allergies, and mother's smoking. On the other hand, we had to approach 1,188 families to obtain interviews from 457 controls: 598 families were no longer living at the address listed in the files, 53 had a confidential telephone number, 49 were known cases of asthma, 21 refused to participate, and 10 were not fluent in French or English.

Parents of 82 cases and 102 controls (20 percent of the study subjects) were asked if they would have their child wear the passive monitoring badge. Parents of two cases and five controls refused, and parents of 61 cases (61/80, 76.2 percent) and 79 controls (79/97, 81.4 percent) returned the badge.

RESULTS

All results for environmental factors (except for nitrogen dioxide, as explained above) are based on the presence or absence in the home of a given risk factor throughout the period between birth and the case's calendar date of diagnosis.

Child allergies (odds ratio (OR) = 1.88, 95 percent confidence interval (CI) 1.27–2.77) and eczema (OR = 2.06, 95 percent CI 1.37–3.10), each adjusted for the other, were independent risk factors for asthma. The percentages of parents and siblings with asthma and the prevalence of past infectious diseases for cases and controls are shown in table 1, along with matched odds ratios adjusted for child allergies and eczema. There were more cases than controls with a family history of asthma, as well as past pneumonia and tonsillectomy. All odds ratios were statistically significant.

Similar results for chemical, physical, and biologic factors in the home are shown in table 2. Slightly more case mothers than control mothers smoked, but the reverse was true for fathers. The adjusted odds ratio for a mother's smoking more than 20 cigarettes daily in comparison with not smoking was increased, at 1.60, and was almost significant ($p = 0.06$). There were twice as many other smokers in the homes of cases as in the homes of controls, and the odds ratio associated with this variable was significantly increased.

In analyses for which results are not shown, we derived a score based on the number of cigarettes smoked daily and the duration of the habit during the period between birth and time of diagnosis. Since smoking habits did not vary much, this analysis did not substantially change the results shown above.

The odds ratios for nitrogen dioxide increased with each categorized level in comparison with the baseline category. In the subgroup tested with the sampler, only six families had a gas stove. However, five of these six were in the highest category of

TABLE 1. Prevalence of a family history of asthma and past infectious diseases, matched odds ratios adjusted for allergy and eczema, and 95% confidence intervals among 457 cases diagnosed with asthma and 457 controls matched for age and area of residence, Montreal, Quebec, Canada, 1988–1990

Factor*	Cases (n = 457) (%)	Controls (n = 457) (%)	Matched odds ratio	95% confidence interval
Father with asthma	8.7	2.8	2.86	1.51–5.41
Mother with asthma	9.8	5.2	1.89	1.12–3.19
Siblings with asthma	9.6	5.4	1.91	1.15–3.19
Tonsillectomy	4.6	1.7	3.69	1.46–9.36
Pneumonia	24.0	8.3	3.31	2.17–5.06

* Factors are defined as yes versus no

TABLE 2. Prevalence of indoor chemical, physical, and biologic factors, matched odds ratios adjusted for allergy and eczema, and 95% confidence intervals among 457 cases diagnosed with asthma and 457 controls matched for age and area of residence, Montreal, Quebec, Canada, 1988–1990

Factor*	Cases (n = 457) (%)	Controls (n = 457) (%)	Matched odds ratio	95% confidence interval
Mother smoking (cigarettes/day)				
0	59.8	63.3	1.00	
>0 to ≤20	30.2	29.6	1.11	0.82–1.51
>20	9.9	7.0	1.60	0.96–2.65
Father smoking (cigarettes/day)				
0	64.9	60.2	1.00	
>0 to ≤20	32.9	38.0	0.80	0.59–1.09
>20	2.2	1.7	1.20	0.46–3.12
Other smokers in the home	14.2	7.2	2.23	1.37–3.63
NO_2† (ppb)				
0	24.5	39.2	1.00	
>0.5 to ≤10	18.0	43.0	0.75	0.29–1.93
>10 to ≤15	13.1	10.1	2.51	0.75–8.35
>15	44.2	7.5	10.54	3.48–31.89
Gas cooking appliance	6.6	5.2	1.33	0.68–2.58
Kerosene space heater	2.0	2.8	0.67	0.27–1.64
Mineral wool insulation‡	86.6	80.1	1.67	0.98–2.85
Urea formaldehyde foam insulation§	2.2	1.9	1.26	0.31–5.17
Fireplace	21.4	24.3	0.82	0.58–1.17
Wood stove	16.6	17.7	0.91	0.62–1.32
Year of construction of first home inhabited by the child‖				
After 1970 versus before	53.4	45.4	1.48	1.10–1.99
After 1980 versus before	20.7	14.0	1.54	1.04–2.29
Electric heating system	86.2	75.9	2.02	1.38–2.94
Central humidifier	8.5	11.8	0.67	0.42–1.07
Central air purifier	14.9	15.6	0.99	0.58–1.69
Central air conditioning	6.7	9.4	0.68	0.41–1.13
Humidifier in child's room	67.6	55.8	1.73	1.28–2.34
Wall-to-wall carpets	56.5	55.3	1.03	0.71–1.50
Dampness on windows	63.6	67.9	0.85	0.58–1.26
Occupant density <1 person/room	77.9	81.6	0.79	0.55–1.12
Pets	43.7	43.5	1.05	0.79–1.38

* Factors are defined as yes versus no if not otherwise specified.
† Based on 61 cases and 79 controls; odds ratio is unmatched.
‡ Based on 202 cases and 221 controls; odds ratio is unmatched.
§ Based on 185 cases and 216 controls; odds ratio is unmatched.
‖ Based on 365 cases and 370 controls.

nitrogen dioxide measurements. The mean ppb value for nitrogen dioxide in the 134 homes without a gas stove was 9.20 (standard deviation, 7.57); in the six homes with a gas stove, it was 17.16 (standard deviation, 8.26).

There was no notable difference between cases and controls with regard to the prevalence of other sources of chemical emissions, such as gas cooking appliances, space heaters, insulating material, fireplaces, and wood stoves. Recently built houses could be sources of more chemicals than older ones; in this study, the risk of developing asthma was greater if the first home inhabited by the child was built more recently than if it was built earlier.

Eighty percent of all study parents reported having a centralized electric heating system in the home, but more cases were exposed to it than controls; a twofold increased risk was associated with having such a system in comparison with not having one. Among the other factors listed in table 2, only the presence of a humidifier in the child's room prior to the time of diagnosis was significantly associated with asthma.

Table 3 shows the association of other personal and socioeconomic factors with asthma. Mother's higher education was a statistically significant risk factor for asthma, and control mothers breast-fed their child slightly more often than case mothers did. Not shown in the table is the distribution of cases and controls according to language spoken at home: among case families, 85.1 percent spoke French, 3.1 percent spoke English, and 11.8 spoke another language. Among control families, these percentages were 80.5, 11.8, and 7.7, respectively. Among mothers of cases, 4.6 percent were 20 years of age or less, as compared with 1.9 percent among mothers of controls. Among case mothers, 76.1 percent were born in Québec, 6.7 percent were born in the West Indies, and 2 percent or less were born in each of 15 other regions. Among controls, 80.9 percent of mothers were from Quebec, 3.9 percent were from the West Indies, 3.7 percent were from Western Europe, and less than 2 percent were from each one of 13 other countries.

In the final conditional logistic regression model, all variables from the above tables, except the ones related to insulation materials, year of home construction, and nitrogen dioxide, were entered into the model. Variables which made an independent contribution ($p \leq 0.05$) and those which were marginally significant ($p \leq 0.10$) are shown in table 4.

Father and sibling asthma were independent risk factors for asthma, as was a past history of pneumonia. Having had a tonsillectomy was associated with an increased risk (OR = 2.83) that was marginally significant ($p \leq 0.06$). A mother's heavy smoking contributed significantly to the incidence of asthma (OR = 2.77), and the presence in the home of smokers other than the parents was associated with an odds ratio of 1.82, which did not quite reach statistical significance ($p = 0.056$). Among the other environmental factors, two were associated with increased and statistically significant odds ratios: the presence of a humidifier in the child's room (OR = 1.89) and having an electric heating system in the home (OR = 2.27). Finally, the absence of breast feeding significantly increased a child's risk of asthma. The mother's having a university education was a marginally significant risk factor ($p \leq 0.07$), whereas the presence of central air conditioning was a protective factor, likewise marginally significant ($p \leq 0.08$).

Multivariate unconditional logistic regression was carried out for the 140 subjects who had nitrogen dioxide measurements; the analysis included nitrogen dioxide and the variables retained in the final conditional model. The odds ratios for the nitrogen dioxide categories (defined as >0.5–10, >10–15, and >15 ppb, in comparison with a zero level) were 0.95 (95 percent CI 0.31–2.95), 3.85 (95 percent CI 0.92–16.09), and 19.87 (95 percent CI 4.75–83.03), respectively.

Among all study children, 52.8 percent attended day-care centers during the study period; thus, our power to detect associa-

TABLE 3. Prevalence of other personal and socioeconomic factors, matched odds ratios adjusted for allergy and eczema, and 95% confidence intervals among 457 cases diagnosed with asthma and 457 controls matched for age and area of residence, Montreal, Quebec, Canada, 1988–1990

Factor*	Cases (n = 457) (%)	Controls (n = 457) (%)	Matched odds ratio	95% confidence interval
Male	55.8	54.0	1.02	0.78–1.33
Mother has university education	23.7	17.8	1.49	1.03–2.13
Father has university education	28.2	24.1	1.21	0.87–1.68
No breast feeding	50.9	47.0	1.24	0.93–1.64

* Factors are defined as yes versus no

TABLE 4. Final conditional logistic regression model* for the analysis of risk factors among 457 cases diagnosed with asthma and 457 controls matched for age and area of residence, Montreal, Quebec, Canada, 1988–1990

Factor†	Odds ratio	95% confidence interval
Child is allergic	2.52	1.50–4.21
Child had eczema	1.68	1.01–2.81
Asthma in father	2.39	1.13–5.04
Asthma in siblings	2.26	1.19–4.29
Child had pneumonia	3.12	1.92–5.09
Child had tonsillectomy	2.83	0.92–8.71
Mother smoking (cigarettes/day)		
>0 to ≤20 versus 0	1.16	0.77–1.76
>20 versus 0	2.77	1.35–5.66
Other smokers in the home	1.82	0.98–3.38
Humidifier in child's room	1.89	1.30–2.74
Electric heating system	2.27	1.41–3.65
Central air conditioning	0.56	0.29–1.08
Mother has university education	1.60	0.96–2.67
No breast feeding	1.47	1.02–2.13

* All variables from tables 1–3 are present in the model (except NO_2, insulation material, and year of construction of the house), but only the odds ratios with p values ≤0.10 are shown.

† Factors are defined as yes versus no, unless otherwise specified.

tions between asthma and environmental exposures encountered in day-care centers was limited. Indeed, none of the estimated odds ratios were statistically significant. However, among cases and controls attending their first day-care center, the risk of asthma was increased when the day-care center had an electric heating system in comparison with other systems (OR = 1.32, 95 percent CI 0.81–2.16); this was also the case for the second day-care center attended (OR = 1.59, 95 percent CI 0.69–3.65).

DISCUSSION

In the literature, there appears to be no other incident density case-control study of new cases of asthma diagnosed by pediatricians among 3- and 4-year-old children. Previous studies were largely cross-sectional in design and included elementary school-aged children (generally aged 6–14 years) who, according to parental reporting, had asthma or a closely related respiratory problem such as wheezing or whistling, or had had some type of chest illness in the previous year. However, most of the potential risk factors for childhood asthma considered in the present report have been studied before. Allergies and eczema were considered as manifestations of atopy, which is strongly associated with asthma in all age groups (9). History of asthma in the family was an independent risk factor in these data, and this is generally consistent with previous findings (10–17). This was also true for pneumonia in infancy (11–13, 18, 19) and tonsillectomy (19).

Many studies have shown a statistically significant relation between passive smoking and childhood asthma (10, 15, 20, 21–28), but more have not (12–14, 16, 18, 19, 29–34). Often, a single variable was used, such as the presence or absence of parental smoking or the presence of one or two smokers, whereas in the present study, the mother's and father's levels of smoking were analyzed separately, in addition to the presence or absence of other smokers (often baby-sitters) in the home. Increased risks in this study may be due to children being younger and belonging to a narrower age group than children in most previous studies and to the physician diagnosis of disease, which is likely to have been much more uniform than that in any other study.

Reduced efficacy of lung defenses and airway injury have been postulated as mechanisms for the effects of nitrogen dioxide on respiratory health (35). From clinical studies, the short-term effects of nitrogen dioxide on asthmatics are not well characterized, although decrements in lung function have been observed. In epidemiologic studies, the focus has mainly been on exposure to nitrogen dioxide in the home environment, and the results are inconclusive. Two studies found a significant association between gas cooking appliances and the prevalence of asthma in children (21, 28), but other studies did not (12, 15, 18, 23, 24, 31–33, 36, 37). When quantitative area sampling measurements of nitrogen dioxide were made in the home using diffusion tubes (22, 34, 37, 38), only once was there an association between nitrogen dioxide in the living room and childhood asthma (22). These inconsistent results are probably due to misclassification of exposure and outcome and to small study sizes (35). The probability of misclassification of residential exposure to nitrogen dioxide has recently been documented (39): It was shown to depend on the number of samples taken and on the categories used to classify results. Having a lesser number of samples was associated with substantial variability when true mean exposure was greater than 15 ppb.

Given these results, misclassification of exposure is likely to have occurred in the present study, wherein only one sample was taken on a subset of 140 subjects. However, a dose-response relation was suggested. This may be due to the use of a personal sampler as opposed to the use of a static sampler in previous studies, and to the likelihood that younger children are more susceptible to increased levels of nitrogen dioxide. In the study by Neas et al. (37), where repeated nitrogen dioxide measurements were made in different rooms with Palmes' passive diffusion tubes, the average nitrogen dioxide value for a household without a major indoor nitrogen dioxide source was 8.6 ppb (standard error, 0.2), whereas it was 23.5 ppb (standard error, 0.4) in homes where a major source existed. These results are quite comparable to those of the present study.

Other studies with different measures of home dampness have consistently found an association with asthma (28, 32, 40–43), with one exception (34). Dampness on windows was the variable used in the present study, and it was probably too vague a measure. Occupant density as a measure of crowding was not significant in this study or in many others (18, 20, 32, 33, 38). Pets are considered a definite risk factor for asthma by clinicians (44); thus, it was surprising to find that only a few studies asked about their presence (14, 28, 33, 38, 40). Moreover, neither in the present study nor in any of the previous studies was there an association between the presence of pets and the incidence of asthma. In this study, at least, the young age of the subjects may explain the negative finding, since younger children may not have had the time to be sensitized.

An interesting finding of this study is that the use of a humidifier in the child's room prior to diagnosis of asthma was strongly associated with the development of asthma. One could interpret these findings as an effect rather than a cause; that is, children with past allergies or past episodes of infection have had previous medical care, and their parents may have been urged to buy a humidifier. Thus, the humidifier use would simply be a proxy for respiratory symptoms that were not yet recognized as asthma. However, we adjusted in the analyses for personal susceptibility, past infections, and family history. Moreover, in the subgroup of 507 children without any allergies or past infections, the unmatched odds ratio for asthma associated with having a humidifier in the child's room was 1.57 (95 percent CI 1.07–2.31).

In another Canadian study, Dekker et al. (28) reported an increased odds ratio associated with the use of a humidifier in the home, but it seems that this variable was use of a central humidifier. In Montreal, winters are long and very cold, and heating systems work continuously; as a result, indoor air is often dry. There is a belief among the lay public that some humidity is necessary for avoiding respiratory illness in children. We can only speculate about the mechanism by which a humidifier may be a risk factor for the development of asthma. Growth of biologic agents in the ducts of the humidifier is one possibility (45, 46). It is also possible that a humidifier could increase the level of house dust mites implicated in the development of asthma (47), since the conditions for their growth are similar to those for fungi (48). However, the outdoor climatic conditions favoring the growth of mites are high humidity and moderate temperature (49), and these conditions are rarely met in Montreal.

Although an electric heating system was never found to be significant in any of the few studies that have considered it as a potential risk factor for childhood asthma (21, 24, 28, 33, 40), it was an independent risk factor in this study. Unfortunately, sample size became too small to determine whether the delivery of heat through forced air, radiant heat, or water radiators modified that effect.

It is not clear why the present study did not find that boys were at increased risk of asthma because many previous studies did (12, 19, 22, 25, 50), although not all (20). Finally, contrary to most studies (14, 19, 25, 40, 50, 51), the present study showed an association between asthma and breast feeding. Only one other study reported that breast feeding was a protective factor (19). The younger age of our study subjects is a likely explanation for these discrepancies. Indeed, the protective effect may not last beyond early infancy.

Misclassification of outcome is a potential concern in most studies of childhood asthma, including this one. However, had many cases not been asthmatics and many controls underdiagnosed, it is unlikely that the study would have shown increased risks for markers of atopy, family history, and previous infections. Potential selection bias needs to be addressed. Controls living in the same census tract were considered a reasonable choice for the study base. However, only families who still resided at the address given in the files were sampled as controls. If the studied factors were associated with mobility, then the proportion of controls exposed to these factors would have been underestimated in this study. There are some indications that this was not the case. For instance, a recent national survey (52) showed that among Quebec women aged 20–44 years in 1986, 37.5 percent were regular smokers, which is identical to the proportion found among control mothers in this study. In addition, in 1983, the prevalence of asthma in 3- and 7-year-old children in Montreal was estimated to be 6.4 percent (53), which is close to the 5.4 percent found among controls in the present study. We also note that socioeconomic factors, which may be associated with mobility, were controlled for in the analysis.

In conclusion, this incident density case-control study showed that even after accounting for personal susceptibility, family history, past infections, and factors related to the indoor environment contribute significantly to the incidence of asthma. For future studies to have a greater impact on public health, it will be necessary to assess exposure-response relations and to relate findings to suggested protective standards. Obtaining reliable quantitative measurements will be the challenge to future studies.

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Populations at Risk
from Particulate Air Pollution — United States, 1992

Despite improvements in air quality since the 1970s, air pollution remains an important environmental risk to human health. A national health objective for the year 2000 is to reduce exposure to air pollutants so that at least 85% of persons live in counties that meet U.S. Environmental Protection Agency (EPA) standards (objective 11.5) (*1*). This report provides estimates from the American Lung Association (ALA) of populations potentially at risk from exposure to particulate air pollution in the United States during 1992.

The National Ambient Air Quality Standard for particulate matter <10 µm in diameter (PM_{10}) is 150 µg/m^3, averaged over 24 hours (*2*). The federal standard is met if this value is not exceeded more than once per calendar year, and the annual arithmetic mean is ≤50 µg/m^3. Information in this report is based on the second highest maximum 24-hour PM_{10} concentrations recorded by at least one monitor in 1992 (EPA, unpublished data, 1993). Both the federal "exceedance" definition (≥155 µg/m^3) and a similar approach applied to the California standard* (≥55 µg/m^3) were used as cutoff values. Estimates of the numbers of persons potentially exposed to levels of PM_{10}

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*California's particulate matter air quality standard of 50 µg/m^3 averaged over 24 hours (*3*) is the most stringent standard in the United States.

above these cutoff values were derived from 1991 census figures for each county (U.S. Bureau of the Census, unpublished data, 1992).

For this report, a population at risk was defined as persons who have a "significantly higher probability of developing a condition, illness, or other abnormal status," as described by EPA (*4*). Five at-risk populations were included: preadolescent children (aged ≤13 years), the elderly (aged ≥65 years), persons aged <18 years with asthma, adults (aged ≥18 years) with asthma, and persons with chronic obstructive pulmonary disease (COPD) (e.g., chronic bronchitis and emphysema). Age-specific county populations for 1991 were estimated by applying the population age distribution of each state (U.S. Bureau of the Census, unpublished data, 1992) to the counties within that state. The number of persons with asthma or COPD in each county was estimated by applying age-specific prevalences from CDC's National Health Interview Survey (*5*) to age-specific population estimates for each county. Although PM_{10} levels are presented on a county basis, they do not indicate that all areas of the county were subject to that level or that all persons in the county were exposed to the recorded concentration.

During 1992, PM_{10} levels were ≥155 µg/m^3 in 16 counties; an estimated 23 million persons (9.1% of the total U.S. population) resided in these counties (Table 1). Approximately 92 million additional persons (36% of the U.S. population) resided in counties in which PM_{10} levels were 55 µg/m^3–154 µg/m^3. Overall, an estimated 115 million persons (45% of the U.S. population) resided in counties with PM_{10} levels ≥55 µg/m^3 (Table 1). In the United States during 1992, 46% of persons with asthma lived in communities with levels of particulate air pollution higher than the California standard.

TABLE 1. Estimated number and percentage of the total population and at-risk[*] subgroups residing in counties with particulate air pollution with a diameter of <10 µm (PM_{10}) at levels ≥155 µg/m^3 and ≥55 µg/m^3[†] — United States, 1992[§]

	PM_{10} levels ≥155 µg/m^3		PM_{10} levels ≥55 µg/m^3	
Population at risk	**No.**	**(%)[¶]**	**No.**	**(%)[¶]**
Total population	**22,894,856**	**(9.1)**	**114,671,632**	**(45.5)**
Preadolescent children (aged ≤13 yrs)	4,931,408	(9.5)	23,794,139	(46.0)
Elderly (aged ≥65 yrs)	2,649,477	(8.3)	14,010,297	(44.1)
Persons (aged <18 yrs) with asthma	387,220	(9.5)	1,878,848	(45.9)
Persons (aged ≥18 yrs) with asthma	697,444	(9.1)	3,528,475	(46.2)
Persons with chronic obstructive pulmonary disease[**]	1,243,407	(9.1)	6,263,409	(46.0)

[*] Population-at-risk estimates should not be added to form totals. These categories are not mutually exclusive.

[†] PM_{10} ≥155 µg/m^3 is the federal "exceedance" definition; PM_{10} ≥55 µg/m^3 is the California "exceedance" standard.

[§] The PM_{10} level of the county does not imply responsibility for the disease status of its population.

[¶] Of the total population in the category, the proportion of each population subgroup potentially exposed.

[**] Includes chronic bronchitis and emphysema.

Particulate Air Pollution — Continued

Reported by: P Vigliarolo, Communications Div; S Rappaport, MPH, K Lieber, MPH, A Gorman, Epidemiology and Statistics Div; R White, MST, National Programs Div, American Lung Association, New York. Air Pollution and Respiratory Health Br, Div of Environmental Hazards and Health Effects, National Center for Environmental Health, CDC.

Editorial Note: Particulate matter (e.g., dust, dirt, and smoke) is a complex and varying mixture of substances. Sources include motor-vehicle emissions, factory and utility smokestacks, residential wood burning, construction activity, mining, agricultural tilling, open burning, wind-blown dust, and fire. Some particles are formed in the atmosphere through the condensation or transformation of other chemical substances. Particles with diameters <10 µm pose a greater health risk than larger particles because particles of this size are easily inhaled deep into the lungs.

Increased risks for illness and death have been associated with particulate air pollution at levels comparable to those presented in this report (*6–8*). Acute effects on the respiratory system are well established and include exacerbations of chronic respiratory disease, restrictions in activity, and increases in emergency department visits and hospitalizations for respiratory illness (*8*). Persons with asthma are particularly sensitive to the effects of particulate air pollution (*8*). A national health objective for the year 2000 is to reduce asthma morbidity, measured by a reduction in asthma hospitalizations, from 188 per 100,000 in 1987 to no more than 160 per 100,000 (objective 11.1) (*1*).

The estimates presented in this report underscore the potential public health importance of particulate air pollution. Although levels of airborne particulate pollution declined substantially from 1988 to 1992 (emissions of PM_{10} decreased 8% and air concentrations of PM_{10} decreased 17%) (*9*), continued efforts are required to reduce health risks associated with particulate air pollution. EPA is reviewing technical and scientific information to determine whether the federal ambient air quality standard for particulate matter, established in 1987, should be revised.

ALA recently issued *The Perils of Particulates* (*10*), which includes national and county estimates of populations at potential risk for exposure to particulate air pollution. Copies are available from local offices of the ALA, telephone (800) 586-4872.

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D

Resources: Agencies, Organizations, Services, References, and Tables of Environmental Health Hazards

CONTENTS

INTRODUCTION 911

GOVERNMENT AGENCIES 911

Federal Agencies 912
  Agency for Toxic Substances and Disease Registry 912
  Centers for Disease Control and Prevention 913
  Consumer Product Safety Commission 913
  Department of Energy 913
  Department of Health and Human Services 914
  Environmental Protection Agency 914
  Food and Drug Administration 915
  Health Resources and Services Administration 915
  National Cancer Institute 915
  National Center for Environmental Health 916
  National Institute for Occupational Safety and Health 916
    Project EPOCH-Envi 917
    NIOSH Educational Resource Centers 918
  National Institute of Environmental Health Sciences 919
    Environmental/Occupational Medicine Academic Awards 920
  National Institutes of Health 921
  Nuclear Regulatory Commission 921
  Occupational Safety and Health Administration 922

State Agencies 922
    State Health Departments and Radon Contacts 922

ASSOCIATIONS AND ORGANIZATIONS 928

American Association of Occupational Health Nurses 928
American Association of Poison Control Centers 928
American Board of Medical Toxicology 931
American College of Obstetricians and Gynecologists 931
American College of Occupational and Environmental Medicine 932
    Occupational Physicians Scholarships Fund 932
American College of Preventive Medicine 933
American Lung Association 933
Association of Occupational and Environmental Clinics 933
Association of Teachers of Preventive Medicine 939
Center for Safety in the Arts 939
Committees on Occupational Safety and Health 940
Consortium for Environmental Education in Medicine 940
MotherRisk Program 940
National Association of Physicians for the Environment 941
Pesticide Education Center 941
Physicians for Social Responsibility 941
Society for Occupational and Environmental Health 942
Teratogen Exposure Registry and Surveillance 942
WorldWatch Institute 943

SELECTED TOPICAL RESOURCES 943

COMPUTERIZED INFORMATION SERVICES 944

Internet 944
List Servers 946
Other Gophers Relevant to Environmental Health, Medicine, and Safety 947
Computer-Based Databases 948

GENERAL REFERENCES 950

Books and Reports 950
Curriculum Resources 951

TABLES OF TOXIC CHEMICALS, HEALTH EFFECTS, AND OCCUPATIONAL EXPOSURES 953

Table D-1: Environmental Agents, Their Sources and Potential Exposures, and Adverse Health Effects: Metals and Metallic Compounds, Hydrocarbons, Irritant Gases, Chemical Asphyxiants, and Pesticides 953
Table D-2: Selected Work-Related Diseases, Disorders, and Conditions Associated with Various Agents, Industries, or Occupations: Infections, Malignant Neoplasms, Hematological, Cardiovascular, Pulmonary, Neurological, and Other Disorders 963
Table D-3: Selected Job Categories, Exposures, and Associated Work-Related Diseases and Conditions 969

* * *

INTRODUCTION

For those readers who are interested in learning more about environmental medicine, or have other resource needs related to environmental medicine, this appendix presents names, addresses, and phone numbers of relevant government agencies and professional associations and organizations, as well as information about computerized information services, and a listing of general references. Several lists of medical schools with federally funded environmental health activities are also provided. Finally, three tables are presented that describe (1) selected environmental agents and their associated sources and potential exposures, (2) selected work-related diseases, disorders, and conditions associated with various agents, and (3) selected job categories, exposures, and associated work-related diseases and conditions.

The information presented in this appendix is not intended to be comprehensive or exhaustive, but rather supplemental and complementary.

GOVERNMENT AGENCIES

Throughout our history, numerous federal and state agencies have been created to address the issues related to safety and health in the workplace, as well as the surrounding environment. Federal and state agencies have become increasingly involved in examining and monitoring the impact of the environment on the health of the public. The following list highlights several of the federal and state agencies currently involved in monitoring, evaluating, and protecting the environment and its relation to public health. Each agency is an invaluable source of information and can readily provide additional resources upon one's request. The agencies are listed in alphabetical order with federal organizations first, followed by state agencies.

Federal Agencies

Agency for Toxic Substances and Disease Registry

The Agency for Toxic Substances and Disease Registry (ATSDR) was created by Superfund legislation in 1980 as a part of the U.S. Department of Health and Human Services. ATSDR's mission is to prevent or mitigate adverse human health effects and diminished quality of life resulting from exposure to hazardous substances in the environment. In order to carry out its mission and to serve the needs of the American people, ATSDR conducts activities in public health assessments, health investigations, exposure and disease registry, emergency response, toxicological profiles, health education, and applied research.

ATSDR's Division of Health Education is mandated to assemble, develop, and distribute to the states, medical colleges, physicians, and other health professionals, educational materials on medical surveillance, screening, and methods of diagnosis and treatment of injury or disease related to exposure to hazardous substances. The Division also provides training and education for primary care physicians to diagnose and treat illness caused by hazardous substances and supports curriculum development and applied research in the area of environmental health.

The Division has developed a self-study series called *Case Studies in Environmental Medicine* which uses case studies to guide physicians through the diagnosis and treatment of illnesses related to hazardous substances exposure.

Several projects have also been developed and implemented to advance these goals. Some of the programs are described below:

- State Cooperative Agreements offer funding and assistance to state health departments for developing educational materials and activities in environmental medicine for health care professionals;
- National Association of County Health Officials Environmental Health Project is a cooperative agreement with ATSDR to conduct instructional sessions and develop supporting materials for local health officials and the medical community concerning the communication of health risks from exposure to hazardous substances;
- Project EPOCH-Envi is co-sponsored by ATSDR and the National Institute for Occupational Safety and Health (NIOSH). Through the cooperative agreement, a consortium of medical schools works towards introducing curricula in occupational and environmental medicine in primary care residency programs;
- The National Medical Association (NMA) is the largest organization of African-American physicians in the United States. ATSDR co-sponsors sessions and lectures on environmental health through the NMA's Regional Environmental Workshops. NMA has recognized the seriousness of environmental contamination in minority communities and is now working with ATSDR to provide training in environmental health for its members.

Agency for Toxic Substances and Disease Registry
1600 Clifton Road, N.E.
Mail Stop E-28
Atlanta, GA 30333
(404) 639-0501
Emergencies (404) 639-0615

Centers for Disease Control and Prevention

The Centers for Disease Control and Prevention (CDC) is charged with protecting the public health of the nation by providing leadership and direction in the prevention and control of diseases and other preventable conditions and responding to public health emergencies.

Centers for Disease Control and Prevention
1600 Clifton Road, N.E.
Atlanta, GA 30333
(404) 639-3286

Consumer Product Safety Commission

The Consumer Products Safety Commission provides information on health and safety effects related to consumer products. It has direct jurisdiction over chronic and chemical hazards in consumer products; assists consumers in evaluating the comparative safety of consumer products; develops uniform safety standards for consumer products and minimizes conflicting state and local regulations; and promotes research and investigation into the causes and prevention of product-related deaths, illnesses, and injuries.

Consumer Product Safety Commission
East West Towers
4340 East West Highway
Bethesda, MD 20814
(301) 504-0580
(800) 638-2772

Department of Energy

The Department of Energy (DOE) provides the framework for a comprehensive and balanced national energy plan through the coordination and administration of the energy functions of the federal government. The Department is responsible for long-term, high-risk research and development of energy technology; the marketing of federal power; energy conservation; the nuclear weapons program; energy regulatory programs; and a central energy data collection and analysis program.

The Environment, Safety and Health Office of the DOE provides independent oversight of departmental execution of environmental, occupational safety and health, and nuclear/nonnuclear safety and security laws, regulations, and policies; ensures that departmental programs are in compliance with environmental, health, and nuclear/nonuclear safety protection plans, regulations, and procedures; provides an independent overview and assessment of Department-controlled activities to ensure that safety-impacted programs receive management review; and carries out legal functions of the nuclear safety civil penalty and criminal referral activities mandated by the Price-Anderson Amendments Act.

Department of Energy
1000 Independence Avenue, S.W.
Washington, DC 20585
(202) 586-5000

Department of Health and Human Services

The Department of Health and Human Services (HHS) is the Cabinet-level department of the federal executive branch most concerned with people and most involved with then nation's human concerns. In one way or another—whether it is mailing out social security checks or making health services more widely available—HHS touches the lives of more Americans than any other federal agency. It is literally a department of people saving people, from newborn infants to our most elderly citizens.

Department of Health and Human Services
200 Independence Ave., S.W.
Washington, DC 20201
(202) 679-0257

Environmental Protection Agency

The Environmental Protection Agency (EPA) was established in 1970 in order to permit coordinated and effective governmental action on behalf of the environment. It endeavors to abate and control pollution systematically, by proper integration of a variety of research, monitoring, standard setting, and enforcement activities. As a complement to its other activities, the Agency coordinates and supports research and antipollution activities by state and local governments, private and public groups, individuals, and educational institutions. It also reinforces efforts among other federal agencies with respect to the impact of their operations on the environment, and it is specifically charged with publishing its determinations when those hold that a proposal is unsatisfactory from the standpoint of public health or welfare or environmental quality. In all, the EPA is designed to serve as the public's advocate for a livable environment.

Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460
(202) 260-2090

Food and Drug Administration

The Food and Drug Administration (FDA) inspects manufacturing plants and warehouses, collects and analyzes samples of foods, drugs, cosmetics, and therapeutic devices for adulteration and misbranding. Responsibilities also extend to sanitary preparation and handling of foods, waste disposal on interstate carriers, and enforcement of the Radiation Control Act as related to consumer products. Epidemiological and other investigations are conducted to determine causative factors or possible health hazards involved in adverse reactions or hazardous materials accidents. Investigators are located in resident posts in major cities throughout the country.

Food and Drug Administration
National Headquarters
200 C Street, S.W.
Washington, DC 20204
(301) 443-2410

Health Resources and Services Administration

Health Resources and Services Administration (HRSA) is responsible for general health services and resource issues relating to issues of access, equity, quality, and cost of care. In order to accomplish this goal, the Administration supports states and communities in their efforts to deliver health care to underserved segments of the population; participates in the federal campaign against AIDS; provides leadership in improving the education, distribution, quality, and use of the health professionals needed to staff the nation's health care system; tracks the supply of and requirements for health professionals and addresses their competence through the development of a health practitioner data bank; and strengthens the public health system by working with state and local public health agencies.

Health Resources and Services Administration
5600 Fishers Lane
Rockville, MD 20857
(301) 443-2086

National Cancer Institute

The National Cancer Institute (NCI) conducts and funds research on the causes, diagnosis, treatment, prevention, control, and biology of cancer and the rehabilitation of people with cancer.

NCI also funds projects for innovative and effective approaches to preventing and controlling cancer, establishes multidisciplinary cancer care and clinical research activities in community hospitals, and supports cancer research training, clinical training, continuing education, and career development.

National Cancer Institute
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892
(301) 496-5615
(800) 422-6237/(800) 4CANCER

National Center for Environmental Health

The mission of the National Center for Environmental Health (NCEH) is to promote health and quality of life by preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. To achieve these goals, NCEH directs programs both to prevent the adverse health effects of exposure to toxic substances and to combat the societal and environmental factors that increase the likelihood of exposure and disease. NCEH also works to prevent injuries and diseases resulting from natural or technologic disasters and to prevent birth defects and development disabilities resulting from nutritional deficiencies or exposure to environmental toxins in utero or during early childhood.

National Center for Environmental Health
Mailstop F29
4770 Buford Highway, N.E.
Atlanta, GA 30341-3724
(404) 488-7003

National Institute for Occupational Safety and Health

The National Institute for Occupational Safety and Health (NIOSH) was established by the Occupational Safety and Health Act of 1970 to conduct research on occupational diseases and injuries, respond to requests for assistance by investigating problems of health and safety in the workplace, recommend standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and train professionals in occupational safety and health.

National Institute for Occupational Safety and Health
200 Independence Avenue, S.W.
Washington, DC 20201
(800) 356-4674

NIOSH Technical Information Branch provides a toll-free technical information service (1-800-35-NIOSH) that provides convenient public access to NIOSH and its information resources. Callers may request information about NIOSH activities or about any aspect of occupational safety and health.

NIOSH Technical Information Branch
Robert A. Taft Laboratory
Mail Stop C-19
4676 Columbia Parkway
Cincinnati, OH 45226-1998
(800) 35-NIOSH

Project EPOCH-Envi. In conjunction with ATSDR, NIOSH established Project EPOCH-Envi to provide support and training to medical schools from around the country who wish to implement curricula in occupational and environmental medicine in primary care residency programs. Through this cooperative agreement, Project EPOCH-Envi conducts workshops and training programs for interested medical school faculty. The sessions focus on instructing faculty members how to develop curricula in occupational and environmental medicine.

Project EPOCH-Envi
National Institute for Occupational Safety and Health
Division of Training and Manpower Development
Curriculum Development Branch
Robert A. Taft Laboratories
4676 Columbia Parkway
Cincinnati, OH 45226-1998
(800) 356-4674

In 1992–1993, the following medical schools were involved in Project EPOCH-Envi or represented by faculty members:

University of Arkansas College of Medicine
University of California, San Francisco, School of Medicine
University of Connecticut School of Medicine
University of Florida College of Medicine
University of Miami School of Medicine
Emory University School of Medicine
Medical College of Georgia
Morehouse School of Medicine
University of Illinois College of Medicine at Peoria
University of Illinois College of Medicine at Urbana-Champaign
University of Illinois College of Medicine at Chicago
Loyola University Chicago, Stritch School of Medicine
Southern Illinois University School of Medicine
University of Massachusetts Medical School
University of Missouri, Columbia School of Medicine

Saint Louis University School of Medicine
University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School
Cornell University Medical Center
University of Rochester School of Medicine
State University of New York at Brooklyn College of Medicine
State University of New York at Syracuse College of Medicine
Bowman Gray School of Medicine
Duke University School of Medicine
East Carolina University School of Medicine
University of North Carolina at Chapel Hill School of Medicine
Medical University of South Carolina College of Medicine
University of South Carolina School of Medicine
University of Texas Medical Center at San Antonio
University of Vermont College of Medicine
West Virginia University School of Medicine

NIOSH Educational Resource Centers

The National Institute for Occupational Safety and Health (NIOSH) funds Educational Resource Centers (ERCs) which conduct research and administer graduate training programs in occupational medicine, occupational health nursing, and industrial hygiene and safety. They also provide continuing education programs for safety and health professionals and outreach programs for the community.

ALABAMA
Deep South Center for Occupational Health and Safety
University of Alabama at Birmingham
Elizabeth Murray
Continuing Education
(205) 934-7178

CALIFORNIA
Northern California ERC
Center for Occupational and Environmental Health
University of California at Berkeley
Barbara Plog, Continuing Education
(510) 231-5647

Southern California ERC
University of Southern California
Ramona Cayuela, Continuing Education
(213) 740-3995

ILLINOIS
Illinois ERC
Occupational Health and Safety Center
University of Illinois, Chicago
Leslie Nickels, School of Public Health
(312) 996-7473

MARYLAND
Johns Hopkins ERC
Johns Hopkins University
Department of Environmental Health Sciences
Dr. Jacqueline Corn,
Continuing Education
(410) 955-2609

MASSACHUSETTS
Harvard ERC
Harvard Educational Resource Center
Daryl Bichel, Continuing Education
(617) 432-3314

MICHIGAN
Michigan ERC
University of Michigan
Center for Occupational Health and Safety
Randy Rabourn, Continuing Education
(313) 936-0148

MINNESOTA
Midwest Center for Occupational Health and Safety
University of Minnesota
Jeanne Ayers, Continuing Education
(612) 221-3992

NEW YORK/NEW JERSEY
UMDNJ-Robert Wood Johnson Medical School
Barbara Young, Registrar
(908) 235-5062

NORTH CAROLINA
Occupational Safety and Health ERC
University of North Carolina
Larry Hyde, Continuing Education
(919) 962-2101

OHIO
University of Cincinnati ERC
University of Cincinnati
Department of Environmental Health
Judy Jarrell, Continuing Education
(513) 558-1730

TEXAS
Southwest Center for Occupational Health and Safety
Pam Parker, Continuing Education
(713) 792-4648

UTAH
Rocky Mountain Center for Occupational and Environmental Health
University of Utah
Connie Crandall, Continuing Education
(801 581-5710

WASHINGTON
Northwest Center for Occupational Health and Safety
University of Washington
Jan Schwert, Continuing Education
(206) 543-1069

National Institute of Environmental Health Sciences

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biological environmental agents on human health and well-being. The Institute supports research and training focused on the identification, assessment, and mechanism of action of potentially harmful agents in the environment. Research results form the basis for preventive programs for environmentally-related diseases and for action by regulatory agencies.

The NIEHS currently sponsors several programs available to the medical school community, individual researchers, and other organizations or centers interested in studying the effects of the environment on health and how to better educate medical school students, employees, and the general public about environmental health risks and hazards. Some of the awards are described below:

• The Environmental/Occupational Medicine Academic Award Program was established by the NIEHS to address the need for increased awareness by physicians of the impact of environmental and occupational conditions on illness, injury, and death. The award serves to assist in improving the quality of environmental/occupational medicine curricula and of fostering research careers in occupational medicine.

Environmental/Occupational Medicine Academic Awards
Chief, Environmental Health Resources Branch
Division of Extramural Research and Training
National Institute of Environmental Health Services
P.O. Box 12233
Research Triangle Park, NC 27709
(919) 541-7825

Environmental/Occupational Medicine Academic Awards Recipients of NIEHS' Environmental/Occupational Medicine Academic Awards for 1994 include:

University of California, Davis, School of Medicine
University of California, Irvine, College of Medicine
University of California, San Francisco, School of Medicine
University of Colorado School of Medicine
Yale University School of Medicine
George Washington University School of Medicine
Emory University School of Medicine
Morehouse School of Medicine
University of Iowa College of Medicine
University of Maryland School of Medicine
Harvard Medical School
University of Massachusetts Medical School
Wayne State University School of Medicine
University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School
Mount Sinai School of Medicine
University of Rochester School of Medicine and Dentistry
University of Washington School of Medicine

• Environmental Health Sciences Center Awards provide core support to universities for multidisplinary research in environmental health. Each center serves as national resources for environmental health research and manpower development. Areas of particular interest include: air, water, and food pollution; toxic mechanisms and body defense mechanisms; and the environmental aspects of cancer, birth defects, behavioral anomalies, respiratory and cardiovascular disease and diseases of other organs.

• Superfund Hazardous Substances - Basic Research and Education Program supports research to expand the base of scientific knowledge needed for adequate assessment of exposure and health risks from the release of hazardous substances, reduction in the amount and toxicity of hazardous substances, and ultimately, to prevent adverse human health effects.

- Hazardous Waste Worker Health and Safety Training provides grant support for the development and administration of health and safety training programs for workers and supervisors engaged in activities related to hazardous waste removal, containment, and transportation, or emergency response. In 1991, this program was expanded to include workers involved in generating and transporting hazardous materials and wastes, oil spill cleanup workers and workers involved in the cleanup of nuclear workshops facilities.
- Clinical Investigator Award provides for the development of clinical investigators in the field of environmental health/human toxicology. The award of up to $35,000 per year supports the research development of physicians to work with research teams on problems arising from the exposures of human populations to environmental chemicals.

National Institute of Environmental Health Sciences
P.O. Box 12233
104 T.W. Alexander Drive
Research Triangle, NC 27709
(919) 541-3212

National Institutes of Health

The National Institutes of Health (NIH) is the principal biomedical research agency of the federal government. Its mission is to pursue knowledge to improve human health. To accomplish this goal, the Institute seeks to expand fundamental knowledge about the nature and behavior of living systems, to apply that knowledge to extend the health of human lives, and to reduce the burdens resulting from disease and disability. In the quest of this mission, NIH supports biomedical and behavioral research around the world, trains promising young researchers, and promotes the acquisition and distribution of medical knowledge. Research activities conducted by NIH will determine much of the quality of health care for the future and reinforce the quality of health care currently available.

National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892

Nuclear Regulatory Commission

The Nuclear Regulatory Commission (NRC) licenses and regulates civilian use of nuclear energy to protect health and safety and the environment. This is achieved by licensing persons and companies to build and operate nuclear reactors and other facilities and to own and use nuclear materials. The Commission makes rules and sets standards for these types of licenses. It also carefully inspects the activities of the persons and companies licensed to ensure that they do not violate the safety rules of the Commission.

Nuclear Regulatory Commission
Washington, DC 20555
(301) 492-7000

Occupational Safety and Health Administration

The Occupational Safety and Health Administration (OSHA) was created within the Department of Labor under the Occupational Safety and Health Act of 1970 to enforce national occupational health and safety standards. OSHA encourages employers and employees to reduce workplace hazards, implements new or improved safety and health programs, provides research in occupational safety and health, requires a reporting and recording system to monitor job-related illnesses and injuries, training, develops mandatory job safety and health standards and enforces them effectively, and provides for the development, analysis, evaluation, and approval of state occupational safety and health programs.

Occupational Safety and Health Administration
Office of Administrative Services
200 Constitution Ave., N.W.
Room N-310
Washington, DC 20210
(202) 219-4667

State Agencies

State Health Departments and Radon Contacts

Alabama Department of Public Health
434 Monroe Street
Montgomery, AL 36130
(205) 242-5052
Radon: Montgomery
(800) 582-1866
(205) 242-5315

Alaska Division of Public Health
Department of Health and Social Services
P.O. Box H
Juneau, AK 99811
(907) 465-3090
Radon: Juneau
(800) 478-4845
(907) 465-3019

Arizona Department of Health Services
1740 W. Adams Street
Phoenix, AZ 85007
(602) 542-1024
Radon: Phoenix
(602) 255-4845

Arkansas Department of Health
4815 W. Markham Street
Little Rock, AR 72205
(501) 661-2111
Radon: Little Rock
(501) 661-2301

California Department of Health Services
714 P Street
Sacramento, CA 95814
(916) 657-1425
Radon: Sacramento
(916) 324-2208

Colorado Department of Health
4210 E. 11th Avenue
Denver, CO 80220
(303) 331-4600
Radon: Denver
(800) 846-3986
(303) 692-3057

Connecticut Department of Health Services
150 Washington Street
Hartford, CT 06106
(203) 566-2038
Radon: Hartford
(203) 566-3122

Delaware Division of Public Health
Department of Health and Social Services
P.O. Box 637
Dover, DE 19903
(302) 739-4701
Radon: Dover
(302) 739-3787
(800) 554-4636 (In-state)

District of Columbia Department of Human Services
Commission of Public Health
1660 L Street, N.W., 12th Floor
Washington, D.C. 20036
(202) 673-7700
Radon: Washington, D.C.
(202) 727-7221

Florida Health Office
Department of Health and Rehabilitation Services
1323 Winewood Blvd.
Building 1
Tallahassee, FL 32301
(904) 487-2705
Radon: Orlando
(904) 488-1525
(800) 543-8279

Georgia Division of Public Health
878 Peachtree Street
Atlanta, GA 30309
(404) 894-7505
Radon: Atlanta
(404) 894-6644

Guam Public Health and Social Services
P.O. Box 2816
Agana, Guam 96910
(671) 734-2083

Hawaii Department of Health
1250 Punchbowl Street
P.O. Box 3378
Honolulu, HI 96801
(808) 586-4410
Radon: Honolulu
(808) 543-4383

Idaho Division of Health
Department of Health and Welfare
450 W. State Street
Boise, ID 83720
(208) 334-5945
Radon: Boise
(800) 445-8647
(208) 334-6584

Illinois Department of Public Health
535 W. Jefferson Street
Springfield, IL 62761
(217) 782-4977
Radon: Springfield
(800) 325-1245
(217) 786-6384

Indiana Board of Health
P.O. Box 1964
1330 W. Michigan Street
Indianapolis, IN 46206
(317) 633-8400
Radon: Indianapolis
(317) 633-0150
(800) 272-9723 (In-state)

Iowa Department of Public Health
Robert Lucas State
Office Building
East 12th and Walnut Streets
Des Moines, IA 50319
(515) 281-5605
Radon: Des Moines
(515) 281-7781
(800) 383-5992 (In-state)

Kansas Department of Health and Environment
900 SW Jackson
Topeka, KS 66612
(913) 296-1522
Radon: Topeka
(913) 296-1560

Kentucky Department for Health Services
Cabinet for Human Resources
275 E. Main Street
Frankfort, KY 40621
(502) 564-3970
Radon: Frankfort
(502) 564-3700

Louisiana Department of Health and Hospitals
P.O. Box 629
Baton Rouge, LA 70821
(504) 342-9500
Radon: Baton Rouge
(800) 256-2494
(504) 925-7042

Maine Bureau of Health
Department of Human Services
State House Station 11
Augusta, ME 04333
(207) 289-2736
Radon: Augusta
(800) 232-0842
(207) 789-5689

Maryland Department of Health and Mental Hygiene
201 W. Preston Street
Baltimore, MD 21201
(301) 225-6500
Radon: Baltimore
(800) 872-3666
(301) 631-3300

Massachusetts Department of Public Health
150 Tremont Street
Boston, MA 02111
(617) 727-2700
Radon: North Hampton
(413) 586-7525

Michigan Department of Public Health
3423 N. Logan Street
Lansing, MI 48909
(517) 335-8024
Radon: Lansing
(517) 335-8190

Minnesota Department of Health
717 Delaware Street, S.E.
P.O. Box 9441
Minneapolis, MN 55440
(612) 623-5460
Radon: Minneapolis
(612) 627-5012
(800) 798-9050

Mississippi Department of Health
P.O. Box 1700
2423 N. State Street
Jackson, MS 39215
(601) 960-7634
Radon: Jackson
(800) 626-7739
(601) 354-6657

Missouri Department of Health
P.O. Box 570
Jefferson City, MO 65102
(314) 751-60001
Radon: Jefferson City
(314) 751-6083
(800) 669-7236 (In-state)

Montana Department of Health and Environmental Sciences
Cogswell Building
Helena, MT 59620
(406) 444-2544
Radon: Helena
(406) 444-3671

Nebraska Department of Health
301 Centennial Mall S.
P.O. Box 95007
Lincoln, NE 68509
(402) 471-4047
Radon: Lincoln
(402) 471-2168
(800) 334-9491 (In-state)

Nevada Health Division
505 E. King Street
Carson City, NV 89710
(702) 687-4740
Radon: Carson City
(702) 687-5394

New Hampshire Division of Public Health Services
Health and Welfare Building
Hazen Drive
Concord, NH 03301
(603) 271-4500
Radon: Concord
(603) 271-4674

New Jersey Department of Health
CN 360
Trenton, NJ 08625
(609) 292-7837
Radon: Trenton
(609) 987-6396
(800) 648-0394

New Mexico Health and Environmental Department
1190 South Francis Drive
Santa Fe, NM 87503
(505) 827-2613
Radon: Santa Fe
(505) 827-4300

New York Department of Health
Tower Building
Empire State Plaza
Albany, NY 12237
(518) 474-2011
Radon: Albany
(518) 458-6451

North Carolina Department of Environment
Health and Natural Resources
Division of Health Services
P.O. Box 27687
Raleigh, NC 27611
(919) 733-4984
Radon: Raleigh
(919) 571-4141

North Dakota Department of Health and Consolidated Labs
State Capitol Judicial Wing
600 E. Boulevard Avenue
Bismarck, ND 58505
(701) 224-2372
Radon: Bismarck
(701) 224-2348

Ohio Department of Health
246 N. High Street
Columbus, OH 43266
(614) 466-2253
Radon: Columbus
(614) 644-2727
(800) 523-4439 (In-state)

Oklahoma Department of Health
1000 NE 10th Street
P.O. Box 53551
Oklahoma City, OK 73152
(405) 271-4200
Radon: Oklahoma City
(405) 271-5221

Oregon State Health Division
1400 SW 5th Avenue
Portland, OR 97201
(503) 229-4032
Radon: Portland
(503) 731-4014

Pennsylvania Department of Health
P.O. Box 90
Harrisburg, PA 17108
(717) 787-6436
Radon: Harrisburg
(717) 787-2480
(800) 23-RADON (In-state)

Puerto Rico Department of Health
Building A, Call Box 70184
San Juan, PR 00936
(809) 766-1616
Radon: Rio Piedras
(809) 767-3563

Rhode Island Department of Health
Cannon Health Building
3 Capitol Hill
Providence, RI 02908
(401) 277-2231
Radon: Providence
(401) 277-2438

South Carolina Department of Health and Environmental Control
2600 Bull Street
Columbia, SC 29201
(803) 735-4880
Radon: Columbia
(800) 768-0362
(803) 734-4700

South Dakota Department of Health
445 E. Capitol
Pierre, SD 57501
(605) 773-3361
Radon: Pierre
(605) 773-3351

Tennessee Department of Health and Environment
344 Cordell Hull Building
Nashville, TN 37247-0101
(615) 741-3111
Radon: Nashville
(800) 232-1139
(615) 741-3651

Texas Department of Health
1100 W. 49th Street
Austin, TX 78756
(512) 458-7111
Radon: Austin
(512) 834-6688

Utah Department of Health
288 N. 1460 W.
P.O. Box 16700
Salt Lake City, UT 84116
(801) 538-6111
Radon: Salt Lake City
(801) 538-6734

Vermont Department of Health
P.O. Box 70
60 Main Street
Burlington, VT 05402
(802) 863-7280
Radon: Montpelier
(800) 640-0601
(802) 828-2886

Virgin Island Department of Health
L18 Sugar Estate
St. Thomas, VI 00802
(809) 774-4888

Virginia Department of Health
P.O. Box 2448
Richmond, VA 23218
(804) 786-3561
Radon: Richmond
(800) 468-0138
(804) 786-5932

Washington Department of Health
1112 S.E. Quince Street
Olympia, WA 98504-7890
(206) 753-5871
Radon: Olympia
(800) 323-9727
(206) 753-4518

West Virginia Department of Public Health
Building 3, State Capital Complex
Charleston, WV 25305
(304) 348-2971
Radon: South Charleston
(304) 558-3526
(800) 922-1255 (In-state)

Wisconsin Division of Health
Department of Health and Social Services
P.O. Box 309
Madison, WI 53707
(608) 266-1511
Radon: Madison
(608) 267-4795

Wyoming Health and Medical Services
Hathaway Building
Cheyenne, WY 82002
(307) 777-6464
Radon: Cheyenne
(800) 458-5847
(307) 777-6015

ASSOCIATIONS AND ORGANIZATIONS

American Association of Occupational Health Nurses

The American Association of Occupational Health Nurses (AAOHN) is an organization of registered professional nurses employed by business and industrial firms; nurse educators, nurse editors, nurse writers; and others interested in occupational health nursing.

American Association of Occupational Health Nurses
50 Lenox Pointe
Atlanta, GA 30324
(800) 241-8014
(404) 262-1162

American Association of Poison Control Centers

The American Association of Poison Control Centers (AAPCC) aids in the procurement of information on the ingredients and potential acute toxicity of substances that may cause accidental poisonings and on the proper management of such poisonings. The AAPCC has established standards for the poison information and control centers, offering immediate information through hotlines around the country. The AAPCC also conducts educational programs and prepares visual aids on prevention of accidental poisonings; maintains a national poisoning database; and operates a nationwide speakers' bureau.

American Association of Poison Control Centers
3800 Reservoir Road, N.W.
Washington, DC 20007
(202) 784-4666/362-7217
(202) 784-2530 FAX

ALABAMA
Birmingham
Regional Poison Control Center
The Children's Hospital of Alabama
Emergency (205) 939-9201
(800) 292-6678 (In-state)
(205) 933-4050

ARIZONA
Phoenix
Samaritan Regional Poison Center
(602) 253-3334

Tucson
Arizona Poison and Drug Information Center
Emergency (800) 362-0101 (In-state)
(602) 626-6016

CALIFORNIA
Fresno
Fresno Regional Poison Control Center
Valley Children's Hospital
Emergency (800) 346-5922 (In-state)
(202) 445-1222

Sacramento
University of California, Davis
Medical Center Regional Poison
Control Center
Emergency (916) 734-3692
(800) 342-9293 (In-state)

San Diego
San Diego Regional Poison Control
Center
University of California, San Diego
Medical Center
Emergency (619) 543-6000
(800) 876-4766 (In-state)

San Francisco
San Francisco Bay Area Regional Poison
Control Center
San Francisco General Hospital
Emergency (800) 523-2222

San Jose
Santa Clara Valley Medical Center
Regional Poison Center
Emergency (408) 299-5112
(800) 342-9293 (In-state)

COLORADO

Denver
Rocky Mountain Poison and Drug
Center
Emergency (303) 629-1123

DISTRICT OF COLUMBIA

Washington
National Capital Poison Control Center
Georgetown University Hospital
Emergency (202) 625-3333
(202) 784-4660 (TTY)

FLORIDA

Tampa
The Florida Poison Information Center
and Toxicology Resource Center
Tampa General Hospital
Emergency (813) 253-444
(800) 282-3171 (In-state)

GEORGIA

Atlanta
Georgia Poison Center
Grady Memorial Hospital
Emergency (800) 282-5846 (In-state)
(404) 616-9000

INDIANA

Indianapolis
Indiana Poison Center
Methodist Hospital of Indiana
Emergency (800) 382-9097 (In-state)
(317) 929-2323

MARYLAND

Baltimore
Maryland Poison Center
Emergency (410) 528-7701
(800) 492-2414 (In-state)

MASSACHUSETTS

Boston
Massachusetts Poison Control System
Emergency (617) 232-2120
(800) 682-9211

MICHIGAN

Detroit
Poison Control Center
Emergency (313) 745-5711

MINNESOTA

Minneapolis
Hennepin Regional Poison Center
Hennepin County Medical Center
Emergency (612) 347-3141
(612) 337-7474 (TTY)

MISSOURI
St. Louis
Cardinal Glennon Children's Hospital Regional Poison Center
Emergency (314) 772-5200
(800) 366-8888 (In-state)

MONTANA
Denver (Colorado)
Rocky Mountain Poison and Drug Center
Emergency (303) 629-1123

NEBRASKA
Omaha
The Poison Center
Emergency (402) 390-5555
(800) 955-9119 (In-state)

NEW JERSEY
Newark
New Jersey Poison Information and Education System
Emergency (800) 962-1253 (In-state)

NEW MEXICO
Albuquerque
New Mexico Poison and Drug Information Center
Emergency (505) 843-2551
(800) 432-6866 (In-state)

NEW YORK
Mineola
Long Island Regional Poison Control Center
Winthrop University Hospital
Emergency (516) 542-2323

New York
New York City Poison Control Center
New York City Department of Health
Emergency (212) 340-4494
(212) P-O-I-S-O-N-S
(212) 689-9014 (TDD)

Nyack
Hudson Valley Poison Center
Nyack Hospital
Emergency (800) 336-6997
(914) 353-1000

OHIO
Columbus
Central Ohio Poison Center
Emergency (614) 228-1323
(800) 682-7625
(614) 228-2272 (TTY)

Cincinnati
Cincinnati Drug and Poison Information Center and Regional Poison Control System
Emergency (513) 558-5111
(800) 872-5111

OREGON
Portland
Oregon Poison Center
Oregon Health Sciences University
Emergency (503) 494-8968
(800) 452-7165 (In-state)

PENNSYLVANIA
Philadelphia
The Poison Control Center
One Children's Center
Emergency (215) 386-2100

Pittsburgh
Pittsburgh Poison Center
Emergency (412) 681-6669

Hershey
Central Pennsylvania Poison Center
Milton S. Hershey Medical Center
Emergency (800) 521-6110

RHODE ISLAND
Providence
Rhode Island Poison Center
Emergency (401) 277-5727
(401) 277-8062 (TDD)

TEXAS
Dallas
North Texas Poison Center
Emergency (214) 590-5000
(800) 441-0040 (In-state)

Galveston
Texas State Poison Center
The University of Texas Medical Branch
Emergency (409) 765-1420
(713) 654-1701 (Houston)
(512) 478-4490 (Austin)

UTAH
Salt Lake City
Utah Poison Control Center
Emergency (801) 581-2151
(800) 456-7707 (In-state)

VIRGINIA
Charlottesville
Blue Ridge Poison Center
Emergency (804) 924-5543
(800) 451-1428

Northern Virginia
National Capital Poison Center
Georgetown University Hospital
Emergency (202) 625-3333
(202) 784-4660 (TTY)

WEST VIRGINIA
Charleston
West Virginia Poison Center
Emergency (800) 642-3625 (In-state)
(304) 348-4211

WYOMING
Omaha (Nebraska)
The Poison Center
Emergency (402) 390-5555
(800) 955-9199 (NE and WY only)

American Board of Medical Toxicology

The American Board of Medical Toxicology (ABMT) evaluates and certifies physicians in medical toxicology and administers certifying examinations to qualified licensed physicians during sessions at annual meetings.

American Board of Medical Toxicology
777 East Park Drive
P.O. Box 820
Harrisburg, PA 17105-8820
(717) 558-7750

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (ACOG) is dedicated to the advancement of women's health through education, advocacy, practice, and research. ACOG works to serve as a strong advocate for quality health care for women, maintain the highest standards of clinical practice and continuing education for its members, promote patient education and stimulate patient understanding of, and involvement in, medical care, and increase awareness among its members and the public of the changing issues facing women's health care.

American College of Obstetricians and Gynecologists
409 12th Street, S.W.
Washington, DC 20024
(202) 638-5577

American College of Occupational and Environmental Medicine

The American College of Occupational and Environmental Medicine (ACOEM) is an association of approximately 6,500 physicians attempting to educate members and other physicians, employers, other organizations, and the public-at-large about occupational and environmental health. The ACOEM has developed a continuing education course entitled *Core Curriculum in Environmental Medicine* in order to enhance physicians' critical thinking on environmental issues, improve their problem-solving skills, and make them more effective at decision-making about environmental concerns. Once the *Curriculum* has been fully developed, ACOEM will make the teaching materials available to other organizations, including medical schools. The ultimate goal of this project has been to enable health professionals to serve as environmental educators to all of the communities in which they are involved.

American College of Occupational and Environmental Medicine
55 West Seegers Road
Arlington Heights, IL 60005
(708) 228-6850

Occupational Physicians Scholarships Fund

The Occupational Physicians Scholarship Fund was established in 1988 to provide support to students entering the occupational health specialty field in their postdoctoral medical education over a ten year period (ending in 1998). The Fund intends to help address the acute shortage of occupational health specialists by supporting up to 100 outstanding postdoctoral students through their residency training. The awards for 1993 ranged from $25,000 to $31,000 for each participant.

Occupational Physicians Scholarship Fund
55 West Seegers Road
Arlington Heights, IL 60005

American College of Preventive Medicine

The American College of Preventive Medicine (ACPM) is a professional society of medical doctors specializing in preventive medicine, public health, aerospace medicine, and occupational medicine committed to educating physicians and students about the latest discoveries in disease prevention and health promotion. As a part of their charge to educate medical students, ACPM offers several core curriculum guidelines and inventories of knowledge and skills related to preventive medicine. In relation to occupational and environmental medicine, ACPM offers a core curriculum, competencies, and performance indicators for preventive medicine residency graduates.

American College of Preventive Medicine
1015 15th Street, N.W.
Suite 403
Washington, DC 20005
(202) 789-0003

American Lung Association

The American Lung Association (ALA) is a federation of state and local associations of physicians, nurses, and laymen interested in the prevention and control of lung disease. The Association works with other organizations in planning and conducting programs in community services, public, professional, and patient education, and research. The ALA also makes recommendations regarding medical care of respiratory disease, occupational health, hazards of smoking, and air conservation.

American Lung Association
1740 Broadway
New York, NY 10019-4374
(212) 315-8700

Association of Occupational and Environmental Clinics

The Association of Occupational and Environmental Clinics is dedicated to higher standards of patient-centered, multi-disciplinary care emphasizing prevention and total health through information sharing, quality service and collaborative research. As a national network of clinical facilities, the clinics vary greatly in orientation, physical facilities, and staff capabilities. However, every clinic does offer an on-site staff physician with either board-certification or demonstrated expertise in occupational medicine. Clinics must also have industrial hygienists and other professionals with expertise in occupational and/or environmental health such as nurses, social workers, and health educators either on staff or available through a pre-arranged referral network.

Association of Occupational and Environmental Clinics
1010 Vermont Avenue, #513
Washington, DC 20005
Contact: Edmund Kelly
Executive Director
(202) 347-4976

ALABAMA

Birmingham
Occupational and Environmental
Medicine Clinic
University of Alabama at Birmingham
Contact: Timothy J. Key, MD, MPH
Brian G. Forrester, MD, MPH
(205) 934-7303

CALIFORNIA

Davis
Occupational and Environmental Health
Clinic
University of California at Davis
Contact: Stephen McCurdy, MD, MPH
Marc Schenker, MD, MPH
(916) 752-3317

Irvine
Occupational and Environmental Clinic
University of California at Irvine
Contact: Dean Baker, MD, MPH
(714) 824-8641

San Francisco
Occupational and Environmental
Medicine Clinic
University of California at San Francisco
Contact: Patricia Quinlan, MPH
Diane Liu, MD, MPH
Jordan Rinker, MD, MPH
(415) 885-7770

COLORADO

Denver
Occupational and Environmental
Medicine Division
National Jewish Center for Immunology
and Respiratory Medicine
Contact: Peggy Mroz, MSPH
Kathleen Kreiss, MD
Cecile Rose, MD, MPH
(303) 398-1520

CONNECTICUT

Farmington
University of Connecticut
Occupational and Environmental
Medicine Program
Contact: Eileen Storey, MD, MPH
(203) 679-2893

New Haven
Yale University Occupational/
Environmental Medicine Program
Yale School of Medicine
Contact: Mark Cullen, MD, MPH
(203) 785-5885

Waterbury
Waterbury Occupational Health
Contact: Gregory McCarthy, MD, MPH
(203) 573-8114

DISTRICT OF COLUMBIA

Washington DC
Division of Occupational and Environmental Medicine
George Washington University School of Medicine
Contact: Laura Welch, MD, MOH
Rosemary Sokas, MD
(202) 994-1734

GEORGIA

Atlanta
Environmental and Occupational Program
The Emory Clinic at Perimeter
Contact: Howard Frumkin, MD, DrPH
Edward Galaid, MD, MPH
(404) 727-3697
(404) 248-5478

ILLINOIS

Chicago
Managed Care Occupational Health Program
Mount Sinai Hospital Medical Center
Contact: Gene Miller, Director
Edward Mogabgab, MD
(312) 257-6480

Occupational Medicine Clinic
Cook County Hospital
Contact: Stephen Hessl, MD, MPH
(312) 633-5310

University of Illinois Occupational Medicine Program
Contact: Linda Forst, MD, MS, MPH
Stephen Hessl, MD, MPH
(312) 996-1063

IOWA

Iowa City
University of Iowa Occupational Medicine Clinic
Department of Internal Medicine College of Medicine
Contact: David Schwartz, MD, DrPH
Emma Rosenau, MPH
(319) 356-8269

KENTUCKY

Lexington
University of Kentucky Occupational Medicine Program
Contact: Terence R. Collins, MD, MPH
Chaim Cohen, MD, MPH
(606) 257-5166

LOUISIANA

New Orleans
Ochsner Center for Occupational Health
Contact: Peter G. Casten, MD, MPH
Douglas A. Swift, MD, MSPH
(504) 838-3955

MAINE

Portland
Center for Health Promotion
Contact: Stephen Shannon, DO, MPH
Sue Upshaw, MD, MPH
(207) 774-7751

MARYLAND

Baltimore
Johns Hopkins University
Center for Occupational and Environmental Health
Contact: Edward J. Bernacki, MD, MPH
(410) 550-2322

Occupational Health Project
School of Medicine
Division of General Internal Medicine
University of Maryland
Contact: James Keogh, MD
Julie Gordon, ScM
(410) 706-7464

MASSACHUSETTS

Boston
Pulmonary Associates
(Occupational Medicine)
Contact: L. Christine Oliver, MD, MPH
Elisha Atkins, MD
Dean Hashimoto, MD, JD
David Christiani, MD, MPH
(617) 726-3741

Cambridge
Occupational and Environmental Health Center
Cambridge Hospital
Contact: Rose Goldman, MD, MPH
Susan Rosenwasser, MEd
(617) 498-1580

South Braintree
Center for Occupational and Environmental Medicine
Massachusetts Respiratory Hospital
Contact: Diane Plantamura, MSW
(617) 848-2600

Worcester
Occupational Health Program
Department of Family and Community Medicine, University of Massachusetts
Contact: Glenn Pransky, MD, Occ.H.
Thomas Hicks, MD, MPH
(508) 856-3093

MICHIGAN

Ann Arbor
Occupational Health Program
School of Public Health
University of Michigan
Contact: David Garabrant, MD, MPH
Tom Robins, MD, MPH
Alfred Franzblau, MD, MPH
(313) 764-2594

Detroit
Division of Occupational Health
Wayne State University
Department of Family Medicine
Contact: Raymond Demers, MD, MPH
Mark Upfal, MD, MPH
James Blessman, MD, MPH
Maryjean Schenk, MD, MPH
Robert Morris, MD, MPH
Sushil Mankani, MD, MPH
(313) 577-1420

East Lansing
Michigan State University
Department of Medicine
Contact: Kenneth Rosenman, MD, MPH
(517) 353-1846

Lansing
Occupational Health Service
St. Lawrence Hospital and Health Institute
Contact: R. Michael Kelly, MD, MPH
(517) 377-0309

Southfield
Center for Occupational and Environmental Medicine
Contact: Margaret Green, MD, MPH
Michael Harbut, MD, MPH
(313) 559-6663

MINNESOTA

Minneapolis

Columbia Park Medical Group
Occupational Medicine Department
Contact: Donald Johnson, MD, MPH
Dorothy Quick, RN, COHN
(612) 572-5710

St. Paul

Ramsey Clinic
Occupational and Environmental Health and Occupational Medicine Residency Training
Contact: Paula Geiger, Admin. Secretary
William H. Lohman, MD
(612) 221-3771

NEW JERSEY

Piscataway

Environmental and Occupational Health Clinical Center
Environmental and Occupational Health Sciences Institute
UMDNJ-Robert Wood Johnson Medical School
Contact: Howard Kipen, MD, MPH
Gail Buckler, RN, MPH, COHN
(908) 445-0123

NEW YORK

Latham

Eastern NY Occupational Health Program
Contact: Anne Tencza, RN, COHN
Eckhardt Johanning, MD, MSc
(518) 783-1518

New York

Bellevue Occupational and Environmental Health Clinic
Bellevue Hospital
Contact: George Friedman-Jimenez, MD
Rafael de la Hoz, MD, MPH
(212) 561-4572

Mount Sinai
J. Selikoff Occupational Health Clinical Center
Contact: Stephen Mooser, MPH
Stephen Levin, MD
Robin Herbert, MD
(212) 241-6173

Rochester

Finger Lakes Occupational Health Services
Contact: Julie R. Cataldo, Administrator
(716) 275-1335

Stony Brook

Center for Occupational and Environmental Medicine
State University of NY School of Medicine
Contact: Wajdy Hailoo, MD, MPH
(516) 444-2167

Syracuse

Central New York Occupational Health Clinical Center
Contact: Michael B. Lax, MD, MPH
(315) 432-8899

NORTH CAROLINA

Durham

Division of Occupational and Environmental Medicine
Duke University Medical Center
Contact: Dennis Darcey, MD, MPSH
Gary Greenberg, MD, MPH
(919) 286-3232

OHIO

Cincinnati

Center for Occupational Health
Holmes Hospital
Contact: James Donovan, MD, MS
Douglas Linz, MD, MS
Susan Pinney, PhD
(513) 558-1234

Greater Cincinnati Occupational Health Center
Jewish Hospital at Evendale
Contact: Harriet Applegate, Director
Margaret Atterbury, MD, MPH
(513) 769-0561

Cleveland
Occupational/Environmental Health Clinic
Department of Family Medicine
MetroHealth Medical Center
Contact: Kathleen Fagan, MD, MPH
(216) 778-8087

OKLAHOMA
Oklahoma City
University Occupational Health Sciences
Division of Occupational and Environmental Medicine
Contact: David Paul, MD, MPH
Lynn Mitchell, MD, MPH
(405) 271-6177

Tulsa
WorkMed, Inc.
Contact: James W. Small, MD, MPH
Steve Snyder, MD
Tiari A. Harris, MD, MPH
Lloyd Anderson, MD
(918) 627-4646

PENNSYLVANIA
Philadelphia
Occupational Health Service
Department of Community and Preventive Medicine
Medical College of Pennsylvania
Contact: Eddy Bresnitz, MD, MS
Harriet Rubenstein, JD, MPH
(215) 842-6540

Pittsburgh
Occupational and Environmental Medicine Program
University of Pittsburgh
Contact: David Tollerud, MD, MPH
(412) 624-3155

Willow Grove
Center for Occupational and Environmental Health
Abington Memorial Hospital
Contact: Jessica Herzstein, MD, MPH
(215) 881-5904

RHODE ISLAND
Pawtuckett
Memorial Hospital of Rhode Island
Occupational Health Service
Brown University
Contact: David G. Kern, MD, MPH
(401) 729-2859

TEXAS
Tyler
Texas Institute of Occupational Safety and Health
Contact: Jeffrey Levin, MD, MSPH
(903) 877-7262

UTAH
Salt Lake City
Rocky Mountain Center for Occupational and Environmental Health
Contact: Anthony Suruda, MD, MPH
Royce Moser, MD, MPH
(801) 581-5056

WASHINGTON
Seattle
Occupational Medicine Program
University of Washington
Harborview Medical Center
Contact: Scott Barnhart, MD, MPH
Drew Brodkin, MD, MPH
Matt Keifer, MD, MPH
(206) 223-3005

WEST VIRGINIA
Huntington
Division of Occupational and Environmental Health
Department of Family and Community Medicine
Marshall University School of Medicine
Contact: Chris McGuffin, MS
James Becker, MD
(304) 696-7045

CANADA
Edmonton, Alberta
Occupational Medicine Consultation Clinic
University of Alberta
Contact: Linda Cocchiarella, MD, MPH
Tee Guidotti, MD, MPH
(403) 492-7849

Manitoba, Winnipeg
MFL Occupational Health Centre, Inc.
Contact: Judy Cook, Executive Director
(204) 949-0811

Association of Teachers of Preventive Medicine

The Association of Teachers of Preventive Medicine (ATPM) is a national organization for medical educators, practitioners, and students committed to advancing the teaching of all aspects of preventive medicine. The scope of knowledge and competence distinctive to preventive medicine includes biostatistics, epidemiology, administration, environmental and occupational health, the application of social and behavioral factors in health and disease, and primary, secondary, and tertiary prevention measures within clinical medicine. ATPM was founded in 1942 with three basic objectives: (1) advancing medical education; (2) developing instruction, scientific skills and knowledge in preventive medicine; and (3) exchanging experience and ideas among its members.

Association of Teachers of Preventive Medicine
1015 15th Street, N.W.
Suite 405
Washington, DC 20005
(202) 682-1698

Center for Safety in the Arts

The Center for Safety in the Arts (CSA) seeks to gather and disseminate information about health hazards encountered by artists, craftsmen, teachers, children, and others working with art materials. The Center provides on-site assessments of the health and safety features of facilities used by artists, craftsmen, and students; responds to inquiries concerning art-related health hazards; and conducts consultation programs. CSA now offers extensive information through a gopher. To tap into gopher to tmn.com, choose the Arts Wire option, followed by the Center for Safety in the Arts options.

Center for Safety in the Arts
5 Beekman Street
New York, NY 10038
(212) 227-6220

Committees on Occupational Safety and Health

The Committees on Occupational Safety and Health are non-profit coalitions of local unions and individual workers, physicians, lawyers, and other health safety activists dedicated to the right of each worker to a safe and healthy job. Committees throughout the states provide health and safety training, technical assistance, consultations and on-site evaluations, and contract language assistance.

Committees on Occupational Safety and Health
275 Seventh Avenue
New York, NY 10001
(212) 627-3900

Consortium for Environmental Education in Medicine

The Consortium for Environmental Education in Medicine was established in 1994 as a non-profit organization committed to developing strategies to improve and enhance the education of physicians on the environment and health. The organization has developed pilot programs for curriculum and faculty development which would seek to make the relationship of environment to health an integral part of undergraduate and post-graduate education.

Consortium for Environmental Education in Medicine (CEEM)
P.O. Box 9132
Waltham, MA 02254-9132
(617) 893-4610

MotherRisk Program

The MotherRisk Program will counsel callers about the safety of an exposure to drugs, chemicals, or radiation during pregnancy or breast-feeding. The team of physicians and information specialists gives advice on whether medications, X-rays, or chemicals in the work environment will harm the developing fetus or breast-fed baby.

MotherRisk Program
Hospital for Sick Children
555 University Avenue
Toronto, Ontario, Canada M5G1X8
(416) 813-6780

National Association of Physicians for the Environment

The National Association of Physicians for the Environment (NAPE) was developed to work with the national medical specialties and subspecialties, with national, state, and local medical societies, and with individual physicians to deal with the impacts of environmental pollutants on the organs, systems, or diseases processes.

National Association of Physicians for the Environment
6410 Rockledge Drive
Suite 203
Bethesda, MD 20817-1809
(301) 571-9791

Pesticide Education Center

Founded in 1933 to educate the public about the hazards and health effects of pesticides, the Pesticide Education Center works with community groups, workers, individuals, and others harmed by or concerned about risks to their health from exposure to pesticides used in agriculture, the home and garden, and other environmental and industrial uses. Its goal is to provide critical information about pesticides so that the public can make more informed decisions and choices. The PEC provides information, curricular materials, and help with seminars and workshops on a nationwide basis.

Pesticide Education Center
P.O. Box 420870
San Francisco, CA 94142-0870
(415) 391-8511

Physicians for Social Responsibility

Physicians for Social Responsibility (PSR) is committed to achieving a sustainable environment. Its environmental program—which complements its work on eliminating weapons of mass destruction and handgun violence—consists of research, advocacy, professional and public education, and international projects designed to protect public health from the effects of toxic pollution and environmental degradation. PSR has also developed a Global Environmental Task Force to help organize informational conferences around the country.

Founded in 1961, PSR is a leading national organization of over 20,000 health professional and supporters working in 90 chapters throughout the U.S. It is the U.S. affiliate of IPPNW, recipient of the 1985 Nobel Peace Prize.

Physicians for Social Responsibility
1101 14th Street, N.W.
Suite 700
Washington, DC 20005
(202) 898-0150

Society for Occupational and Environmental Health

The Society for Occupational and Environmental Health (SOEH) includes scientists, academicians, and industry and labor representatives who seek to improve the quality of both working and living places by operating as a neutral forum for conferences involving all aspects of occupational and environmental health. SOEH's activities include studying specific categories of hazards, as well as developing methods for assessment of health effects and diseases associated with particular jobs.

Society for Occupational and Environmental Health
6728 Old McLean Village Drive
McLean, VA 22101
(703) 556-9222

Teratogen Exposure Registry and Surveillance

The Teratogen Exposure Registry and Surveillance (TERAS) is a network of geneticists and pathologists studying human embryos and fetuses exposed to teratogens. TERAS maintains information networks for consultation and evaluations.

Teratogen Exposure Registry and Surveillance
Frederick Bieber, PhD
Director
Department of Pathology
Brigham and Women's Hospital
75 Francis Street
Boston, MA
(617) 732-6507

WorldWatch Institute

The WorldWatch Institute is a research organization that aims to encourage a reflective and deliberate approach to global problem-solving. The Institute seeks to anticipate global problems and social trends and to focus attention on emerging global issues, including population growth, family planning, environmental degradation, and renewable energy options.

WorldWatch Institute
1776 Massachusetts Avenue, N.W.
Washington, DC 20036
(202) 452-1999

SELECTED TOPICAL RESOURCES

AIR POLLUTION
American Lung Association
(212) 315-8700
EPA Clean Air Act
(202) 382-7548

ART SUPPLIES
Center for Safety in the Arts
(212) 277-6220

ASBESTOS
EPA Asbestos Programs
(800) 368-5888

CANCER INFORMATION
National Cancer Institute
(800) 4-CANCER
EPA Carcinogen Assessment Group
(202) 382-5898

CHEMICAL EMERGENCIES
Chemical Spills Emergency Hotline
(800) 535-0202
EPA Hazardous Waste Hotline
(800) 535-0202
ATSDR Emergency Hotline
(404) 639-6300

CONSUMER PRODUCT SAFETY
Consumer Product Safety Commission
(800) 638-2772

HAZARDOUS WASTE
EPA Emergency Planning and Community Right to Know Hotline
(800) 535-0202
Integrated Risk Information System (IRIS)
(202) 475-6743
IRIS User Support
(513) 569-7254
Superfund Records of Decision
(703) 920-9810
State Health Departments

LEAD
National Center for Environmental Health (CDC)
(404) 488-4880
National Lead Information Center
(800) LEAD-FYI
Child and Maternal Health Clearinghouse
(202) 625-8410

LUNG DISEASE
American Lung Association
(212) 315-8700
LUNGLINE/National Jewish Hospital
(800) 222-5864

OCCUPATIONAL HEALTH

National Institute for Occupational Safety and Health
(800) 356-4674
Occupational Safety and Health Administration
(202) 219-8151

PESTICIDES

EPA National Pesticides Hotline
(800) 535-PEST
National Pesticide Telecommunications Network
(800) 858-7378

POISONING

Poison Control Centers

PREGNANCY CONCERNS

MotherRisk Program
(416) 813-7378

RADON

EPA Office of Radon Programs
(202) 475-9605
National Radon Hotline
(800) SOS-RADON
State Health Departments

SMOKE

American Lung Association
(212) 315-8700

TOXIC SUBSTANCES

American Chemical Society's Chemical Referral Center
(202) 887-1315
ATSDR Emergency Response Branch
(404) 639-6300
ATSDR Toxicological Profiles
(404) 639-6000
EPA Toxic Substances Control Act (TSCA) Information Line
(202) 554-1404
EPA Toxic Chemical Release Inventory System
(800) 535-0202

WATER

EPA Safe Drinking Water Hotline
(800) 426-4791

COMPUTERIZED INFORMATION SERVICES

Computerized information services have become a valuable link in providing users with up-to-date information, resources, and opportunities for interaction with others interested in similar topics. The following list is by no means comprehensive, but merely provides points of access to relevant information and communication list-servers.

Internet

Department of Energy's Environment, Safety, and Health Technical Information Service

In 1993, DOE released its new computer-based information service, called the Environment, Safety, and Health Technical Information Service (TIS). TIS is designed to provide the DOE community with technical information that is reliable, current, and easy to use. Eventually, TIS will replace the current Safety Performance Measurement System (SPMS). For more information, please address any questions to the TIS Helpline at (208) 526-8955 or send e-mail to support@tis.inel.gov.

Electronic Green Journal

The ELECTRONIC GREEN JOURNAL is a professional refereed publication from the University of Idaho devoted to disseminating information concerning sources of international environmental topics including: assessment, conservation, development, disposal, education, hazards, pollution, resources, technology, and treatment. The journal serves communities as an educational environmental resource, and includes both practical and scholarly articles, bibliographies, reviews, editorial comments, and announcements. The journal is currently available via gopher, worldwide web, or ftp. Subscriptions are being planned for the future. To tap into the journal through gopher, type gopher.uidaho.edu and choose University of Idaho Electronic Publications; to tap in through World-Wide Web (WWW) type http://gopher.uidaho.edu/ 1/UI_gopher/library/egj/; or to tap in through ftp, type ftp.uidaho.edu.

EnviroLink Network

The Envirolink Network is a non-profit organization that is dedicated to facilitating communication on environmental issues. The network is composed of over 400,000 people in 93 countries. The Network has recently created a new network entitled EnviroFreenet. EnviroFreenet offers e-mail accounts, environmental billboards, chat conferences, the EnviroGopher, the EnviroWeb, and access to almost every other Internet Service available. The network can be accessed using either telnet or gopher. EnviroFreenet can be reached through telnet with the address envirolink.org. Directions then follow. If you have access to gopher, go to the main gopher list and choose international organizations and then choose "EnviroGopher," followed by "Connect to EnviroFreenet" or gopher to: envirolink.org port 70.

HazDat

The HazDat system is a scientific and administrative database developed by ATSDR to provide rapid access to information on the release of hazardous substances from Superfund sites or from emergency events and on the effects of these substances on the health of human populations. The source documents used for the initial development of HazDat include environmental and health data contained in Agency products and in other non-Agency site characterization documents as appropriate. ATSDR's products include health assessments and supporting documentation for over 1,200 sites, toxicological profiles for over 150 substances, and more than 2,000 health consultations. ATSDR staff enter data into HazDat on a continuing basis. HazDat is available to the public over the Internet through a World-Wide Web (WWW) server. Access can be gained through: http://atsdr1.atsdr.cdc.gov:8080/atsdrhome.html.

Medical List—A Guide to On Line Medical Resources

The Medical List provides a complete listing of Internet resources connected with health, disease, therapy, and clinical medicine. This resource list is offered in text form as The Medical List and as Medical Matrix—a hypertest database accessible using World Wide Web browsers like Mosaic. The Medical List is the text of Healthmatrix—a Windows Help, icon drive, hypertext presentation of the database. For more information, call (209) 466-6878.

Gopher access to The Medical List is available at the URL:(Uniform Resource Locator)gopher://una.hh.lib.umich.edu:70/11/inetdirs/sciences/medclin:malet. Gopher allows key word searching and e-mail of this document to any Internet address. Access can also be gained through ftp—frp2.cc.ukans.edu pub/hmatrix/ and get file medlst94.txt or medlst94.zip.

Medical Matrix is a project of the Internet Working Group of the American Medical Informatics Association. Medical Matrix uses icons and keyword searches to locate on line medical resources. Access can be gained through: http://kuhttp.cc.ukans.edu/cwis/units/medcntr/Lee/HOMEPAHE.HTML.

WHO Global Environmental Epidemiology Network, GEENET

The Network was established in 1987 as a means for the World Health Organization to strengthen education, training and research in institutions involved in epidemiological teaching and research on the health effects of environmental hazards, and other epidemiological applications in environmental and occupational health.

The Network aims at improved communication and collaboration between institutions in this field in developed and developing countries. A series of documents with information of value for training and research development is prepared for the Network and lists of Network members are distributed on a regular basis. Training and research promotion workshops are organized in collaboration with national and international agencies.

For more information, write: WHO GEENET, Environmental Epidemiology, World Health Organization, 1211 Geneva, Switzerland.

List Servers

Air Pollution and Biology

The address is mailbase@mailbase.ac.uk; and you can join by sending the message join airpollution-biology Firstname Lastname and your address.

EHS-L Environmental Health Systems

The address is listserv@ALBNYDH2; and you can join by sending the message subscribe EHS-L Firstname Lastname and your address.

ENVBEH-L Environment and Human Behavior

The address is listserv@POLYVM; and you can join by sending the message subscribe ENVBEH-L Firstname Lastname and your address.

Enviroethics

The address is mailbase@mailbase.ac.uk; and you can join by sending the message join enviroethics Firstname Lastname and your address.

Occup-Env Med List (Occupational and Environmental Medicine Listing on Internet)

Occupational and environmental medicine represents a growing clinical and public health discipline, seeking to evaluate and prevent the diseases and health effects that may be related to exposures at work and from other environments. The Occup-Env Med Mail-list provides a moderated forum for announcements, dissemination of text files and academic discussion. The forum is designed to allow presentation of clinical vignettes, synopses of new regulatory issues and reports of interesting items from publication elsewhere (both the medical and the non-medical journals).

To subscribe, send a message of: subscribe occ-env-med-l "first name last name" to occ-env-med-l@mc.duke.edu.

To post a message send the message to: occ-env-med-l@duke.edu

PBLIST/PBL-LIST (Problem-Based Listing on Internet)

PBLIST is devoted to problem-based learning and related methods in health care education. PBL-LIST covers a broader discussion of problem-based learning in general throughout all disciplines. To subscribe to either of these lists, send a one line e-mail message of:

SUB PBL-LIST Your first name Your last name
to: LISTSERV@eng.monash.edu.au

One can also communicate with other list members by sending mail to PBL-LIST@eng.monash.edu.au

Other Gophers Relevant to Environmental Health, Medicine, and Safety

Center for Safety in the Arts

gopher://tmn.com to reach the CSA gopher and then choose the Arts Wire option, followed by the Center for Safety in the Arts

Division of Environmental Health and Safety

gopher://romulus.ehs.uiuc.edu:70/11

The Environmental Magazine

gopher://gopher.internet.com:2100/11/collected/d

National Institute of Environmental Health Sciences (NIEHS)

gopher://gopher.niehs.nih.gov/1

U.S. Environmental Protection Agency

gopher://gopher.rtpnc.epa.gov/1

Computer-Based Databases*

The National Library of Medicine (NLM) is the world's largest research library in a single scientific or professional field. The library collects materials in all major areas of the health sciences, as well as in such areas as chemistry, physics, botany, and zoology.

The Library's computer-based Medical Literature Analysis and Retrieval System (MEDLARS) and toxicology (TOXLINE) databases provide on-line bibliographic access to the Library's store of bio-medical information. For information about access to MEDLARS and TOXLINE services, contact: MEDLARS Management Section, National Library of Medicine, 8600 Rockville Pike, Bethesda, MD 20894, (301) 496-1131, (800) 638-8480 (outside Maryland).

Primary biomedical data bases included on the MEDLARS system are:

MEDLINE indexes articles from over 3200 biomedical journals published in the US and abroad. MEDLINE is indexed using NLM's controlled vocabulary, MESH (Medical Subject Headings), and contains all citations indexed in INDEX MEDICUS. Produced by the National Library of Medicine.

TOXLINE is designed to offer comprehensive bibliographic coverage of toxicological information. It covers the pharmacological, biochemical, physiological, environmental, and toxicological effects of chemicals and drugs. Produced by Specialized Information Services of the National Library of Medicine.

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* Murdock, BS, ed. 1991. *Environmental Issues in Primary Care.* Minnesota: Minnesota Department of Health.

TOXNET (Toxicology Data Network) is a computerized system of toxicological data banks operated by the National Library of Medicine, and is part of the broader MEDLARS system.

The TOXNET software consists of modules to build, edit, and review the records of constituent data banks.

CCRIS (Chemical Carcinogenesis Research Information System) is a factual data bank sponsored by the National Cancer Institute. It contains data derived from both short- and long-term bioassays on approximately 1200 chemicals.

ETICBACK (Environmental Teratology Information Center Backfile) is a bibliographic data base covering teratology and development toxicology.

TRI (Toxic Chemical Release Inventory) contains information on the annual estimated releases of toxic chemicals to the environment in the United States. These data include the names and addresses of the facilities and the amounts of certain toxic chemicals they release to the air, water, or land or transfer to waste sites.

HSDB (Hazardous Substances Data Bank) is a comprehensive data base containing records for over 4100 toxic or potentially toxic chemicals. It contains information in such areas as toxicity, environmental fate, human exposure, chemical safety, waste disposal, emergency handling, and regulatory requirements.

IRIS (Integrated Risk Information System) is an on-line data base built by the Environmental Protection Agency (EPA). It contains EPA carcinogenic and noncarcinogenic health risk and regulatory information on about 400 chemicals. For more information, call (513) 569-7254.

RTECS (Registry of Toxic Effects of Chemical Substances) contains toxic effects data for approximately 100,000 chemicals. It is built and maintained by the National Institute for Occupational Safety and Health (NIOSH). Acute and chronic effects are covered in such areas as skin/eye irritation, carcinogenicity, mutagenicity, and reproductive consequences.
Contact: (800) 35-NIOSH

DIRLINE (NLM's Directory of Information Resources on-line) is an on-line database containing information on approximately 15,000 organizations that provide information and services directly to requesters. DIRLINE is available on-line through the MEDLARS system and can also be searched with GRATEFUL MED software.
Contact: (301) 496-1131

Various software packages are available for access to MEDLARS, including:

GRATEFUL MED, a microcomputer software interface that assists users in performing on-line searches of NLM's databases. GRATEFUL MED can be bought from the National Technical

Information Service (NTIS)

CHEMLEARN (NTIS), an interactive, microcomputer-based training package for CHEMLINE. Produced by Specialized Information Services of the National Library of Medicine, it runs on IBM-PC/XT/AT/PS/2 compatibles. CHEMLEARN is available from NTIS, product number PB88-218144. For more information on the contents of the software, call (301) 496-1131.

TOXLEARN is an interactive, microcomputer-based training package for TOXLINE. Its menu-driven structure allows users to make choices in learning about basic aspects of TOXLINE. It contains approximately four hours of interactive instruction and is produced by the Specialized Information Services of the National Library of Medicine. TOXLEARN runs on IBM-PC compatibles and is available from NTIS, product number PB88-155766. For more information on the contents of the software, call: (301) 496-1131.

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Books and Reports

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TABLES OF TOXIC CHEMICALS, HEALTH EFFECTS, AND OCCUPATIONAL EXPOSURES

TABLE D-1: Environmental Agents, Their Sources and Potential Exposures, and Adverse Health Effects: Metals and Metallic Compounds, Hydrocarbons, Irritant Gases, Chemical Asphyxiants, and Pesticides

Agent	Exposure	Route of Entry	Systems(s) Affected	Primary Manifestations	Aids in Diagnosis	Remarks
Metals and Metallic Compounds						
Arsenic	Alloyed with lead and copper for hardness; manufacturing of pigments, glass, pharmaceuticals; byproduct in copper smelting; insecticides; fungicides; rodenticides; tanning	Inhalation and ingestion of dust and fumes	Neuromuscular	Peripheral neuropathy, sensory-motor	Arsenic in urine	
			Gastrointestinal	Nausea and vomiting, diarrhea, constipation		
			Skin	Dermatitis, finger and toenail striations, skin cancer, nasal septum perforation		
			Pulmonary	Lung cancer		
Arsine	Accidental byproduct of reaction of arsenic with acid; used in semiconductor industry	Inhalation of gas	Hematopoietic	Intravascular hemolysis: hemoglobinuria, jaundice, oliguria or anuria	Arsenic in urine	
Beryllium	Hardening agent in metal alloys; special use in nuclear energy production; metal refining or recovery	Inhalation of fumes or dust	Pulmonary (and other systems)	Granulomatosis and fibrosis	Beryllium in urine (acute); Beryllium in tissue (chronic); chest x ray; immunologic tests (such as lymphocyte transformation) may also be useful	Pulmonary changes virtually indistinguishable from sarcoid on chest x ray

Continued

TABLE D-1: Continued

Agent	Exposure	Route of Entry	System(s) Affected	Primary Manifestations	Aids in Diagnosis	Remarks
Cadmium	Electroplating; solder for aluminum; metal alloys, process engraving; nickel-cadmium batteries	Inhalation or ingestion of fumes or dust	Pulmonary Renal	Pulmonary edema (acute); Emphysema (chronic) Nephrosis	Urinary protein	Also a respiratory tract carcinogen
Chromium	In stainless and heat-resistant steel and alloy steel; metal plating; chemical and pigment manufacturing; photography	Percutaneous absorption, inhalation, ingestion	Pulmonary Skin	Lung cancer Dermatitis, skin ulcers, nasal septum perforation	Urinary chromate (questionable value)	
Lead	Storage batteries; manufacturing of paint, enamel, ink, glass, rubber ceramics, chemical industry	Ingestion of dust, inhalation of dust or fumes	Hematologic Renal Gastrointestinal Neuromuscular CNS Reproductive	Anemia Nephropathy Abdominal pain ("colic") Palsy ("wrist drop") Encephalopathy, behavioral abnormalities Spontaneous abortions (?)	Blood lead Urinary ALA Zinc protoporphyrin (ZPP); free erythrocyte protophyrin (FEP)	Lead toxicity, unlike that of mercury, is believed to be reversible, with the exception of late renal and some CNS effects.
Mercury (Elemental)	Electronic equipment; paint; metal and textile production; catalyst in chemical manufacturing; pharmaceutical production	Inhalation of vapor; slight percutaneous absorption	Pulmonary CNS	Acute pneumonitis; Neuropsychiatric changes (erethism); tremor	Urinary mercury	Mercury illustrates several principles. The chemical form has a profound effect on its toxicology, as is the case for many metals. Effects of mercury are highly variable. Though inorganic mercury poisoning is primarily renal, elemental and organic poisoning are primarily neurological.

Mercury (continued) (Inorganic)	Agricultural and industrial poisons	Some inhalation and GI and percutaneous absorption	Pulmonary Renal CNS	Acute pneumonitis Proteinuria Variable	Urinary mercury	The responses are difficult to quantify, so dose-response data are generally unavailable. Classic tetrad of gingivitis, sialorrhea, irritability, and tremor is associated with both elemental and inorganic mercury poisoning; the four signs are not generally seen together. Many effects of mercury toxicity, especially those in CNS, are irreversible.
(Organic)		Efficient GI absorption, percutaneous absorption, and inhalation	Skin CNS	Dermatitis Sensorimotor changes, visual field constriction, tremor	Blood and urine mercury, but sensitivity	
Nickel	Corrosion-resistant alloys; electroplating; catalyst production; nickel-cadmium batteries	Inhalation of dust or fumes	Skin Pulmonary	Sensitization dermatitis ("nickel itch") Lung and paranasal sinus cancer		
Zinc oxide	Welding byproduct; rubber manufacturing	Inhalation of dust or fumes that are freshly generated		"Metal fume fever" (fever, chills, and other symptoms)	Urinary zinc (useful as an indicator of exposure, not for acute diagnosis)	A self-limiting syndrome of 24-48 h with apparently no sequelae
Hydrocarbons						
Benzene	Manufacturing of organic chemicals, detergents, pesticides, solvents, paint removers; used as a solvent	Inhalation of vapor; slight percutaneous absorption	CNS Hematopoietic Skin	Acute CNS depression Leukemia, aplastic anemia Dermatitis	Urinary phenol	Note that benzene, as with toluene and other solvents, can be monitored via its principal metabolite.

Continued

TABLE D-1: Continued

Agent	Exposure	Route of Entry	System(s) Affected	Primary Manifestations	Aids in Diagnosis	Remarks
Toluene	Organic chemical manufacturing; solvent; fuel component	Inhalation of vapor, percutaneous absorption of liquid	CNS Skin	Acute CNS depression Chronic CNS problems such as memory loss Irritation dermatitis	Urinary hippuric acid	
Xylene	A wide variety of uses as a solvent; an ingredient of paints, lacquers, varnishes, inks, dyes, adhesives, cements; an intermediate in chemical manufacturing	Inhalation of vapor; slight percutaneous absorption of liquid	Pulmonary Eye, nose, throat CNS	Irritation, pneumonitis, acute pulmonary edema (at high doses) Irritation Acute CNS depression	Methylhippuric acid in urine, xylene in expired air, xylene in blood	
Ketones (Acetone) (Methylethyl ketone-MEK) (Methyl *n*-propyl ketone-MPK) (Methyl *n*-butyl ketone-MBK) (Methyl iso-butyl ketone-MIBK)	A wide variety of uses as solvents and intermediates in chemical manufacturing	Inhalation of vapor, percutaneous absorption of liquid	CNS PNS Skin	Acute CNS depression MBK has been linked with peripheral neuropathy Dermatitis	Acetone in blood, urine, expired air (used as an index for exposure, not for diagnosis)	The ketone family demonstrates how a pattern of toxic responses (that is, CNS narcosis) may feature exceptions (that is, MBK peripheral neuropathy)
Formaldehyde	Widely used as a germicide and a disinfectant in embalming and histopathology, for example, an in the manufacture of textiles, resins, and other products	Inhalation	Skin Eye Pulmonary	Irritant and contact dermatitis Eye irritation Respiratory tract irritation, asthma	Patch testing may be helpful for dermatitis	Recent animal tests have shown it to be a respiratory carcinogen. Confirmatory epidemiologic studies are in progress

Trichloro-ethylene (TCE)	Solvent in metal degreasing, dry cleaning, food extraction; ingredient of paints, adhesives, varnishes, inks	Inhalation, percutaneous absorption	Nervous	Acute CNS depression Peripheral and cranial neuropathy	Breath analysis for TCE	TCE is involved in an important pharmacological interaction. Within hours of ingesting alcoholic beverages, TCE workers experience flushing of the face, neck, shoulders, and back. Alcohol may also potentiate the CNS effects of TCE. The probable mechanism is competition for metabolic enzymes
			Skin	Irritation, dermatitis		
			Cardiovascular	Arrhythmias		
Carbon tetrachloride	Solvent for oils, fats, lacquers, resins, varnishes, other materials; used as a degreasing and cleaning agent	Inhalation of vapor	Hepatic	Toxic hepatitis	Expired air and blood levels	Carbon tetrachloride is the prototype for a wide variety of solvents that cause hepatic and renal damage. This solvent, like trichloroethylene, acts synergistically with ethanol.
			Renal	Oliguria or anuria		
			CNS	Acute CNS depression		
			Skin	Dermatitis		
Carbon disulfide	Solvent for lipids, sulfur, halogens, rubber, phosphorus, oils, waxes, and resins; manufacturing of organic chemicals, paints, fuels, explosives, viscose rayon	Inhalation of vapor, percutaneous absorption of liquid or vapor	Nervous	Parkinsonism, psychosis, suicide Peripheral neuropathies	Iodine-azide reaction with urine (nonspecific since other bivalent sulfur compounds give a positive test); CS_2 in expired air, blood, and urine	A solvent with unusual multisystem effects, especially noted for its cardiovascular, renal, and nervous system actions.
			Renal	Chronic nephritic and nephrotic syndromes		
			Cardiovascular	Acceleration or worsening of atherosclerosis; hypertension		
			Skin	Irritation; dermatitis		
			Reproductive	Menorrhagia and metrorrhagia		

Continued

TABLE D-1: Continued

Agent	Exposures	Route of Entry	System(s) Affected	Primary Manifestations	Aids in Diagnosis	Remarks
Stoddard solvent	Degreasing, paint thinning	Inhalation of vapor, percutaneous absorption of liquid	Skin CNS	Dryness and scaling from defatting; dermatitis Dizziness, coma, collapse (at high levels)		A mixture of primarily aliphatic hydrocarbons, with some benzene derivatives and naphthenes.
Ethylene glycol ethers (Ethylene glycol monoethyl ether-Cellosolve) (Ethylene glycol monoethyl ether acetate-Cellosolve acetate) (Methyl- and butyl-substituted compounds such as ethylene glycol mono-methyl ether-Methyl Cellosolve)	The ethers are used as solvents for resins, paints, lacquers, varnishes, gum, perfume, dyes, and inks; the acetate derivatives are widely used as solvents and ingredients of lacquers, enamels, and adhesives. Exposure occurs in dry cleaning, plastic, ink, and lacquer manufacturing, and textile dying, among other processes.	Inhalation of vapor, percutaneous absorption of liquid	Reproductive, CNS, renal, liver			Ethylene glycol ethers, as a class of chemicals, have been shown in animals to have adverse reproductive effects, including reduced sperm count and spontaneous abortion, as well as CNS, renal, and liver effects.
Ethylene oxide	Used in the sterilization of medical equipment, in the fumigation of spices and other foodstuffs, and as a chemical intermediate	Inhalation	Skin Eye Respiratory tract Nervous system	Dermatitis and frostbite Severe irritation; possibly cataracts with prolonged exposure Irritation Peripheral neuropathy		Recent animal tests have shown it to be carcinogenic and to cause reproductive abnormalities. Epidemiologic studies indicate that it may cause leukemia in exposed workers.

Dioxane	Used as a solvent for a variety of materials, including cellulose acetate, dyes, fats, greases, resins, polyvinyl polymers, varnishes, and waxes	Inhalation of vapor, percutaneous absorption of liquid	CNS Renal Liver	Drowsiness, dizziness, anorexia, headaches, nausea, vomiting, coma Nephritis Chemical hepatitis		Dioxane has caused a variety of neoplasms in animals.
Polychlorinated biphenyls (PCBs)	Formerly used as a di-electric fluid in electrical equipment and as a fire retardant coating on tiles and other products. New uses were banned in 1976, but much of the electrical equipment currently used still contains PCBs	Inhalation, ingestion, skin absorption	Skin Eye Liver	Chloracne Irritation Toxic hepatitis	Serum PCB levels for chronic exposure	Animal studies have demonstrated that PCBs are carcinogenic. Epidemiologic studies of exposed workers are inconclusive.
Irritant Gases						
Ammonia	Refrigeration; petroleum refining; manufacturing of nitrogen-containing chemicals, synthetic fibers, dyes, and optics	Inhalation of gas	Upper respiratory tract	Upper respiratory irritation		Also irritant of eyes and moist skin
Hydrochloric acid	Chemical manufacturing; electroplating; tanning; metal pickling; petroleum extraction; rubber, photographic, and textile industries	Inhalation of gas or mist	Upper respiratory tract	Upper respiratory irritation		Strong irritant of eyes, mucous membranes, and skin
Hydrofluoric acid	Chemical and plastic manufacturing; catalyst in petroleum refining; aqueous solution for frosting, etching, and polishing glass	Inhalation of gas or mist	Upper respiratory tract	Upper respiratory irritation		In solution, causes severe and painful burns of skin and can be fatal
Sulfur dioxide	Manufacturing of sulfur-containing chemicals; food and textile bleach; tanning; metal casting	Inhalation of gas, direct contact of gas or liquid phase on skin or mucosa	Middle respiratory tract	Bronchospasm (pulmonary edema or chemical pneumonitis in high dose)	Chest x ray, pulmonary function tests	Strong irritant of eyes, mucous membranes, and skin

Continued

TABLE D-1: Continued

Agent	Exposure	Route of Entry	System(s) Affected	Primary Manifestations	Aids in Diagnosis	Remarks
Chlorine	Paper and textile bleaching; water disinfection; chemical manufacturing; metal fluxing; detinning and dezincing iron	Inhalation of gas	Middle respiratory tract	Tracheobronchitis, pulmonary edema, pneumonitis	Chest x ray, pulmonary function tests	Chlorine combines with body moisture to form acids, which irritate tissues from nose to alveoli.
Ozone	Inert gas-shielded arc welding; food, water, and air purification; food and textile bleaching; emitted around high-voltage electrical equipment	Inhalation of gas	Lower respiratory tract	Delayed pulmonary edema (generally 6-8 h following exposure)	Chest x ray, pulmonary function tests	Ozone has a free radical structure and can produce experimental chromosome aberrations; it may thus have carcinogenic potential.
Nitrogen oxides	Manufacturing of acids, nitrogen containing chemicals, explosives, and more; byproduct of many industrial processes	Inhalation of gas	Lower respiratory tract	Pulmonary irritation, bronchiolitis fibrosa obliterans ("silo filler's disease"), mixed obstructive-restrictive changes	Chest x ray, pulmonary function tests	
Phosgene	Manufacturing and burning of isocyanates, and manufacturing of dyes and other organic chemicals; in metallurgy for ore separation; burning or heat source near trichloroethylene	Inhalation of gas	Lower respiratory tract	Delayed pulmonary edema (delay seldom longer than 12 h)	Chest x ray, pulmonary function tests	
Isocyanates TDI (toluene diisocyanate) MDI (methylene diphenyldiisocyanate) Hexamethylene diisocyanate and others	Polyurethane manufacture; resin-binding systems in foundries; coating materials for wires; used in certain types of paint	Inhalation of vapor	Predominantly lower respiratory tract	Asthmatic reaction and accelerated loss of pulmonary function	Chest x ray, pulmonary function tests	Isocyanates are both respiratory tract "sensitizers" and irritants in the conventional sense.

Asphyxiant gases Simple asphyxiants: nitrogen hydrogen, methane, and others	Enclosed spaces in a variety of industrial settings	Inhalation of gas	CNS	Anoxia	O_2 in environment	No specific toxic effect; act by displacing O_2
Chemical Asphyxiants						
Carbon monoxide	Incomplete combustion in foundries, coke ovens, refineries, furnaces, and more	Inhalation of gas	Blood (hemoglobin)	Headache, dizziness, double vision	Carboxyhemoglobin	
Hydrogen sulfide	Used in manufacturing of sulfur-containing chemicals; produced in petroleum production; byproduct of petroleum product use; decay of organic matter	Inhalation of gas	CNS Pulmonary	Respiratory center paralysis, hypoventilation Respiratory tract irritation	PaO_2	
Cyanide	Metallurgy, electroplating	Inhalation of vapor, percutaneous absorption, ingestion	Cellular metabolic enzymes (especially cytochrome oxidase)	Enzyme inhibition with metabolic asphyxia and death	SCN in urine	
Pesticides						
Organophophates: malathion, parathion, and others		Inhalation, ingestions, percutaneous absorption	Neuromuscular	Cholinesterase inhibition, cholinergic symptoms: nausea and vomiting, salivation, diarrhea, headache, seating, meiosis, muscle fasciculations, seizures, unconsciousness, death	Refractoriness to atropine; plasma or red cell cholinesterase	As with many acute toxins, rapid treatment of organophosphate toxicity is imperative. Thus, diagnosis is often made based on history and a high index of suspicion rather than on biochemical tests. Treatment is atropine to block cholinergic effects and 2-PAM (2-pyridine-alsoxine methiodide) to reactivate cholinesterase.

Continued

TABLE D-1: Continued

Agent	Exposure	Route of Entry	System(s) Affected	Primary Manifestations	Aids in Diagnosis	Remarks
Carbamates: carbaryl (Sevin) and others		Inhalation, ingestion, percutaneous absorption	Neuromuscular	Same as organophosphates	Plasma cholinesterase; urinary 1-naphthol (index of exposure)	Treatment of carbamate poisoning is the same as that of organophosphate poisoning except that 2-PAM is contra-indicated.
Chlorinated hydrocarbons: chlordane, DDT, heptachlor, chlordecone (Kepone), aldrin, dieldrin, uridine		Ingestion, inhalation, percutaneous absorption	CNS	Stimulation or depression	Urinary organic chlorine, or *p*-chlorophenol acetic acid	The chlorinated hydrocarbons may accumulate in body lipid stores in large amounts.
Bipyridyls: paraquat, diquat		Inhalation, ingestion, percutaneous absorption	Pulmonary	Rapid massive fibrosis, only following paraquat ingestion		An interesting toxin in that the major toxicity, pulmonary fibrosis, apparently occurs only after ingestion.

SOURCE: *Principles and Practice of Environmental Health*, A.B. Tarcher, ed., Plenum, New York, 1992.

TABLE D-2: Selected Work-Related Diseases, Disorders, and Conditions Associated with Various Agents, Industries, or Occupations: Infections, Malignant Neoplasms, and Hematological, Cardiovascular, Pulmonary, Neurological, and Miscellaneous Disorders

Diseases, Disorders, and Conditions	Industry or Occupation	Agent
Infections		
Anthrax	Shepherds, farmers, butchers, handlers of imported hides or fibers, veterinarians, veterinarian pathologists, weavers	*Bacillus anthraces*
Brucellosis	Farmers, shepherds, vets, lab and slaughterhouse workers	*Brucella abortus, suis*
Plague	Shepherds, farmers, ranchers, hunters, field geologists	*Yersinia pestis*
Hepatitis A	Day-care center, orphanage, and mental retardation institution staff, medical personnel	Hepatitis A virus
Hepatitis B	Nurses and aides, anesthesiologists, orphanage and mental institution staffs, medical lab workers, general dentists, oral surgeons, physicians	Hepatitis B virus
Hepatitis C (formerly included in non-A, non-B)	Same as hepatitis A and B	Hepatitis C virus
Ornithosis	Psittacine bird breeders, pet shop and zoo workers, poultry producers, vets	*Chlamydia psittaci*
Rabies	Veterinarians, game wardens, lab workers, farmers, ranchers, trappers	Rabies virus
Rubella	Medical personnel	Rubella virus
Tetanus	Farmers, ranchers	*Clostridium tetani*
Tuberculosis Pulmonary	Physicians, medical personnel, medical lab workers	*Mycobacterium tuberculosis*
Tuberculosis Silicotuberculosis	Quarrymen, sandblasters, silica processors, miners, foundry workers, ceramic industry	Silicon dioxide (silica), *M. tuberculosis*
Tularemia	Hunters, fur handlers, sheep industry, cooks, veterinarians, ranchers, veterinarian pathologists	*Francisella tularensis*

Continued

TABLE D-2: Continued

Diseases, Disorders, and Conditions	Industry or Occupation	Agent
Malignant Neoplasms		
Bladder	Rubber and dye workers	Benzidine, 1- and 2-naphthylamine, auramine, magenta, 4-aminobiphenyl, 4-nitrophenyl
Bone	Dial painters, radium chemists and processors	Radium
Kidney and other urinary organs	Coke oven workers	Coke oven emissions
Liver	Vinyl chloride polymerization industry	Vinyl chloride monomer
Liver hemangiosarcoma	Vintners	Arsenical pesticides
Lung, bronchial, tracheal	Asbestos industry, users	Asbestos
	Topside coke oven workers	Coke oven emissions
	Uranium and flourspar miners	Radon daughters
	Chromium producers, processors, users	Chromates
	Smelters	Arsenic
	Mustard gas formulators	Mustard gas
	Ion-exchange resin makers, chemists	Bis(chloromethyl)-ether, chloromethyl methyl ether
Nasal cavity	Woodworkers, furniture makers	Hardwood dusts
	Boot and shoe industry	Unknown
	Radium chemists and processors, dial painters	Radium
	Chromium producers, processors, users	Chromates
	Nickel smelting and refining	Nickel
		Asbestos
Peritoneal, pleural mesothelioma	Asbestos industry, users	Asbestos
Scrotal	Automatic lathe operators, metalworkers	Mineral, cutting oils
	Coke oven workers, petroleum refiners, tar distillers	Soots and tars, tar distillates
Hematological Disorders		
Agranulocytosis or neutropenia	Workers exposed to benzene	Benzene
	Explosives, pesticide industries	Phosphorous
	Pesticide, pigment, pharmaceutical industries	Inorganic arsenic

TABLE D-2: Continued

Diseases, Disorders, and Conditions	Industry or Occupation	Agent
Anemia Aplastic	Explosives manufacturing	TNT
	Workers exposed to benzene	Benzene
	Radiologists, radium chemists, dial painters	Ionizing radiation
Anemia Hemolytic, nonautoimmune	Whitewashing and leather industry	Copper sulfate
	Electrolytic processes, arsenical ore smelting	Arsine
	Plastics industry	Trimellitic anhydride
	Dye, celluloid, resin industries	Naphthalene
Leukemia Acute lymphoid	Rubber industry	Unknown
	Radiologists	Ionizing radiation
Leukemia Acute myeloid	Workers exposed to benzene	Benzene
	Radiologists	Ionizing radiation
Leukemia Erythroleukemia	Workers exposed to benzene	Benzene
Methemoglobinemia	Explosives, dye industries	Aromatic amino and nitro compounds (e.g., aniline, TNT, nitroglycerin)
Cardiovascular Disorders		
Angina	Auto mechanics, foundry workers, wood finishers, traffic control, driving in heavy traffic	Carbon monoxide
Arrhythmias	Metal cleaning, solvent use, refrigerator maintenance	Solvents, fluorocarbons
Raynaud's phenomenon (secondary)	Lumberjacks, chain sawyers, grinders, chippers	Whole-body or segmental vibration
	Vinyl chloride polymerization	Vinyl chloride monomer
Pulmonary Disorders		
Alveolitis (extrinsic, allergic)	Farmer's lung bagassosis, bird-breeder's lung, suberosis, maltworker's lung, mushroom worker's lung, maple bark disease, cheese-washer's lung, coffee-worker's lung, fish-meal-worker's lung, furrier's lung, sequoiosis, woodworker's lung, miller's lung	Various agents
Asbestosis	Asbestos workers, users	Asbestos

Continued

TABLE D-2: Continued

Diseases, Disorders, and Conditions	Industry of Occupation	Agent
Asthma (extrinsic)	Jewelry, alloy, catalyst makers	Platinum
	Polyurethane, adhesive, paint workers	Isocyanates
	Alloy, catalyst, refinery workers	Chromium, cobalt
	Solderers	Aluminum soldering flux
	Plastic, dye, insecticide makers	Phthalic anhydride
	Foam workers, latex makers, biologists	Formaldehyde
	Printing industry	Gum arabic
	Nickel platers	Nickel sulfate
	Bakers	Flour
	Plastics industry	Trimellitic anhydride
	Woodworkers, furniture makers	Red cedar, wood dusts
	Detergent formulators	Bacillus-derived exoenzymes
	Animal handlers	Animal dander
Beryllium disease (chronic)	Beryllium alloy, ceramic, cathode-ray tube, nuclear reactor workers	Beryllium
Bronchitis, pneumonitis, pulmonary edema (acute)	Refrigeration, fertilizer, oil-refining industries	Ammonia
	Alkali, beach industries	Chlorine
	Silo fillers, arc welders, nitric acid workers	Nitrogen oxides
	Paper, refrigeration, oil-refining industries	Sulfur dioxide
	Cadmium smelters, processors	Cadmium
	Plastics industry	Trimellitic anhydride
Byssinosis	Cotton industry	Cotton, flax, hemp, cotton-synthetic dusts
Pneumoconiosis	Coal miners, bauxite workers	Coal dust, bauxite fumes
Silicosis	Mining, metal, and ceramic industries, quarrymen, sand blasters, silica processors	Silica
Talcosis	Talc processors	Talc
Neurological Disorders		
Cerebellar ataxia	Chemical industry	Toluene
	Electrolytic chlorine production, battery manufacturing, fungicide formulators	Organic mercury
Encephalitis (toxic)	Battery, smelter, foundry workers	Lead
	Electrolytic chlorine production, battery manufacturing, fungicide formulators	Organic, inorganic mercury

TABLE D-2: Continued

Diseases, Disorders, and Conditions	Industry or Occupation	Agent
Neuropathy (toxic and inflammatory)	Pesticide, pigment, pharmaceutical industries	Arsenic, arsenic compounds
	Furniture refinishers, degreasers	Hexane
	Plastic-coated-fabric workers	Methyl butyl ketone
	Explosives industry	TNT
	Rayon manufacturing	Carbon disulfide
	Plastics, hydraulics, coke industries	Tri-o-cresyl phosphate
	Battery, smelter, foundry workers	Inorganic lead
	Dentists, chloralkali workers	Inorganic mercury
	Chloralkali, fungicide, battery workers	Organic mercury
	Plastics, paper manufacture	Acrylamide
Parkinson's disease (secondary)	Manganese processors, battery manufacturing, welders	Manganese
	Internal combustion engine industries	Carbon monoxide
Miscellaneous		
Abdominal pain	Battery manufacturing, enamelers, smelter, painters, ceramics workers, plumbers, welders	Lead
Cataract	Microwave, radar technicians	Microwaves
	Explosives industry	TNT
	Radiologists	Ionizing radiation
	Blacksmiths, glass blowers, bakers	Infrared radiation
	Moth repellent formulators, fumigators	Naphthalene
	Explosives, dye, herbicide, pesticide industries	Dinitrophenol, dinitro-o-cresol
Dermatitis (contact, allergic)	Adhesives, sealants, and plastics industries, leather tanning, poultry dressing, fish packing, boat building and repair, electroplating, metal cleaning, machining, housekeeping	Irritants (cutting oils, solvents, phenol, acids, alkalies, detergents, fibrous glass), allergens (nickel, epoxy resins, chromates, formaldehyde, dyes, rubber products)
Headache	Firefighters, foundry workers, wood finishers, dry cleaners, traffic control, driving in heavy traffic	Carbon monoxide, solvents

Continued

TABLE D-2: Continued

Disease, Disorders, and Conditions	Industry or Occupation	Agent
Hepatitis (toxic)	Solvent users, dry cleaners, plastics industry	Carbon tetrachloride, chloroform,tetrachloroethane trichloroethylene
	Explosives and dye industries	Phosphorous, TNT
	Fire and waterproofing additive formulators	Chloronaphthalene
	Plastics formulators	4,4-Methylene-dianiline
	Fumigators, gasoline and fire-extinguishers formulators	Ethylene dibromide
	Disinfectant, fumigant, synthetic resin formulators	Cresol
Inner ear damage	Various	Excessive noise
Infertility (male)	Formulators	Kepone
	Producers, formulators, applicators	1,2-Dibromo-3-chloropropane
Psychosis (acute)	Gasoline, seed, and fungicide workers, wood preservation, rayon manufacturing	Lead (especially organic), mercury, carbon disulfide
Renal failure (acute, chronic)	Battery manufacturing, plumbers, solderers	Inorganic lead
	Electrolytic processes, arsenical ore smelting	Arsine
	Battery manufacturing, jewelers, dentists	Inorganic mercury
	Fluorocarbon, fire-extinguisher formulators	Carbon tetrachloride
	Antifreeze manufacturing	Ethylene glycol

SOURCE: *Principles and Practice of Environmental Medicine*, Tarcher, AB, ed., Plenum, New York, 1992.

TABLE D-3: Selected Job Categories, Exposures, and Associated Work-Related Diseases and Conditions

Job Categories	Exposures	Work-Related Diseases and Conditions
Agricultural workers	Pesticides, infectious agents, gases, sunlight	Pesticide poisoning, "farmers' lung," skin cancer
Anesthetists	Anesthetic gases	Reproductive effects, cancer
Animal handlers	Infectious agents, allergens	Asthma
Automobile workers	Asbestos, plastics, lead, solvents	Asbestosis, dermatitis
Bakers	Flour	Asthma
Battery makers	Lead, arsenic	Lead poisoning, cancer
Butchers	Vinyl plastic fumes	"Meat wrappers' asthma"
Caisson workers	Pressurized work environments	"Caisson disease," "the bends"
Carpenters	Wood dust, wood preservatives, adhesives	Nasopharyngeal cancer, dermatitis
Cement workers	Cement dust, metals	Dermatitis, bronchitis
Ceramic workers	Talc, clays	Pneumoconiosis
Demolition workers	Asbestos, wood dust	Asbestosis
Drug manufacturers	Hormones, nitroglycerin, etc.	Reproductive effects
Dry cleaners	Solvents	Liver disease dermatitis
Dye workers	Dyestuffs, metals, solvents	Bladder cancer, dermatitis
Embalmers	Formaldehyde, infectious agents	Dermatitis
Felt makers	Mercury, polycyclic hydrocarbons	Mercuralism
Foundry workers	Silica, molten metals	Silicosis
Glass workers	Heat, solvents, metal powders	Cataracts
Hospital workers	Infectious agents, cleansers, radiation	Infections, accidents
Insulators	Asbestos, fibrous glass	Asbestosis, lung cancer, mesothelioma

Continued

TABLE D-3: Continued

Job Categories	Exposures	Work-Related Diseases and Conditions
Jack hammer operators	Vibration	Raynaud phenomenon
Lathe operators	Metal dusts, cutting oils	Lung disease, cancer
Laundry workers	Bleaches, soaps, alkalies	Dermatitis
Lead burners	Lead	Lead poisoning
Miners (coal, hard rock, metals, etc.)	Talc, radiation, metals, coal dust, silica	Pneumoconiosis, lung cancer
Natural gas workers	Polycyclic hydrocarbons	Lung cancer
Nuclear workers	Radiation, plutonium	Metal poisoning, cancer
Office workers	Poor lighting, poorly designed equipment	Joint problems, eye problems
Painters	Paints, solvents, spackling compounds	Neurologic problems
Paper makers	Acids, alkalies, solvents, metals	Lung disorders, dermatitis
Petroleum workers	Polycyclic hydrocarbons, catalysts, zeolites	Cancer, pneumoconiosis
Plumbers	Lead, solvents, asbestos	Lead poisoning
Railroad workers	Creosote, sunlight, oils, solvents	Cancer, dermatitis
Seamen	Sunlight, asbestos	Cancer, accidents
Smelter workers	Metals, heat, sulfur dioxide, arsenic	Cancer
Steel workers	Heat, metals, silica	Cataracts, heat stroke
Stone cutters	Silica	Silicosis
Textile workers	Cotton dust, fabrics, finishers, dyes, carbon disulfide	Byssinosis, dermatitis, psychosis
Varnish makers	Solvents, waxes	Dermatitis
Vineyard workers	Arsenic, pesticides	Cancer, dermatitis
Welders	Fumes, nonionizing radiation	Lead poisoning, cataracts

SOURCE: *Principles and Practice of Environmental Medicine*, A.B. Tarcher, ed., Plenum, New York, 1992.

E

Committee and Staff Biographies

DAVID P. RALL, M.D., Ph.D., (Chairman) is the former Director of the National Institute of Environmental Health Sciences. He received his M.D. and Ph.D. in Pharmacology from Northwestern University. He served as pharmacologist and later chief of the Laboratory of Chemical Pharmacology at the National Cancer Institute, and as Adjunct Professor at the University of North Carolina, Chapel Hill. He has authored and co-authored over 170 published papers relating to comparative pharmacology, cancer chemotherapy, blood-brain barrier, blood CSF barrier, pesticide toxicology, and drug research and regulation. He is a member of the Institute of Medicine, the Society of Toxicology, the American Association of Pharmacology and Experimental Therapeutics, the American Association for Cancer Research, and the Society for Occupational and Environmental Health. He is also a recipient of the Society for Toxicology's Arnold J. Lehman Award.

M. BROWNELL ANDERSON, M.Ed., is Assistant Vice President of Educational Programs for the Association of American Medical Colleges' Division of Educational Policy. Ms. Anderson is responsible for the design, implementation, and maintenance of a database of curriculum and evaluation activities in all 143 medical schools in North America. She is also the Executive Secretariat of the Group on Educational Affairs and the Research in Medical Education Conference Planning Committee; the Project Director of *Assessing Change in Medical Education*, a Charles E. Culpeper Foundation Grant; a Faculty Member for the AAMC's Generalist Education Workshop and Curriculum

Change—Introduction to Problem-Based Learning Workshop; and Executive Secretariat for the Society of Medical College Directors of Continuing Medical Education.

ELIZABETH L. BOWEN, M.D., Ed.D., is an Assistant Professor of Family Medicine and Medical Education at Morehouse School of Medicine in Atlanta, Georgia. Dr. Bowen is also the past president of Physicians for Social Responsibility—the American Chapter of International Physicians for the Prevention of Nuclear War—for which she has traveled across the globe promoting world health and world peace. In 1992, Dr. Bowen was selected to travel to the Earth Summit in Rio de Janeiro as a presenter and medical consultant for the United States. In recognition of her achievements and dedication, the students of Morehouse School of Medicine elected her "Teacher of the Year—1992."

L. THOMPSON BOWLES, M.D., Ph.D., is President of the National Board of Medical Examiners. Dr. Bowles previously served as Vice President for Medical Affairs, Executive Dean, and Professor of Surgery at the George Washington University Medical Center. Dr. Bowles has also been actively involved in examining the status of medical curricula in the United States and the need for flexibility and change to meet the growing needs of the future through numerous publications and presentations. Dr. Bowles is a member of the Institute of Medicine

EDDY A. BRESNITZ, M.D., M.S., is Chairman and Professor of Community and Preventive Medicine and Director of the Division of Occupational and Environmental Medicine at the Medical College of Pennsylvania and Hahnemann University School of Medicine. Dr. Bresnitz is an NHLBI Preventive Pulmonary Academic Awardee (PPAA) and Chair of the PPAA Curriculum Subcommittee. Dr. Bresnitz is a consultant to the ATSDR and serves on the Postgraduate Education Committee of the American Thoracic Society. In addition to research interest in surveillance of environmental and occupational diseases, he has research interests in faculty development in implementing innovations in medical education. He has received a Lindback Foundation Award for Teaching.

MARK R. CULLEN, M.D., is Director of the Occupational and Environmental Medicine Program and Professor of Medicine and Public Health at the Yale University School of Medicine. His research interests include lead, asbestos, isocyanates, multiple chemical sensitivities, and, more generally, the application of biomarkers of effects in epidemiologic studies. Co-author of a major clinical text in OEM, Dr. Cullen is an Academic Awardee in OEM and is a consultant to several major unions, corporations, and governmental agencies.

RICHARD J. JACKSON, M.D., M.P.H., is Chief of the Division of Communicable Disease Control in the California State Department of Health Services. Dr. Jackson previously served as the Chief of the Hazard Identification and Risk Assessment Branch for the California Environmental Protection Agency. Dr. Jackson has also served as an expert advisor to the Centers for Disease Control and Prevention on Childhood Lead Poisoning and for ATSDR on the Training for Primary Care Physicians on Toxicologic Hazards. Dr. Jackson has also written extensively and given congressional testimony on such issues as pesticides in children's diets, risk assessment, and the environmental hazards and impacts on children and reproductive health.

KARL T. KELSEY, M.D., M.O.H., is an Associate Professor of Occupational Medicine in the Occupational Health Program, and an Associate Professor of Radiobiology at the Harvard School of Public Health. Dr. Kelsey has been the principal investigator for the Department of Energy and NIEHS for several projects on ionizing radiation in nuclear medicine and the susceptibility to genetic damage from Butadiene. His other research interests include the use of laboratory methods in epidemiologic research for the study of occupational and environmental mutagen exposures in humans, DNA damage, and cancer risk.

HOWARD M. KIPEN, M.D., M.P.H., is an Associate Professor in the Department of Environmental and Community Medicine and Director of the Division of Occupational Medicine at the Environmental/Occupational Health Sciences Institute of the University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School. His research on sensitivities to low level chemical exposures is supported by the NIEHS. Dr. Kipen has worked extensively on educating physicians and the community on environmental and occupational risks through numerous articles, in addition to making presentations across the country on the role of the environment on health. He serves numerous federal advisory committees, is President of the Occupational and Environmental Medical Association of New Jersey, and is on the board of Directors of the Center for Safety in the Arts. Dr. Kipen is also an Academic Awardee in Environmental and Occupational Medicine from NIEHS.

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EULA BINGHAM, Ph.D., is Professor of Environmental Health in the College of Medicine at the University of Cincinnati. Dr. Bingham also serves as a trustee for the Natural Resources Defense Council and the Greater Cincinnati Occupational Health Clinic. She is also Director of the Ohio Hazardous Substance Institute and is a member of the Institute of Medicine. Her research interests are in environmental health, occupational safety and health, and chemical carcinogenesis. Dr. Bingham has served in numerous public-sector positions including: Department of Labor (Assistant Secretary for Occupational Safety and Health, National Institute for Safety and Health study section), U.S. Food and Drug Administration (Food and Drug Advisory Commission, Environmental Health Advisory Commission), and the U.S. Environmental Protection Agency (Science Advisory Board). Dr. Bingham has also served as a member of several committees and boards for the National Academy of Sciences, National Research Council, and Institute of Medicine. Dr. Bingham is a recipient of the Rockefeller

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ANDREW M. POPE, Ph.D., is a Senior Staff Officer and Study Director in the Institute of Medicine's Division of Health Promotion and Disease Prevention. His interests focus on the human health effects of environmental and occupational exposures, with expertise in physiology, toxicology, and epidemiology. As a Research Fellow in the Division of Pharmacology and Toxicology at the U.S. Food and Drug Administration, Dr. Pope's research focused on the neuroendocrine and reproductive effects of various environmental substances in food-producing animals. During his tenure at the National Academy of Sciences, and since 1989 at the Institute of Medicine, Dr. Pope has directed and edited numerous reports on environmental and occupational issues, such as: biologic markers in reproductive toxicology, neurotoxicology, indoor allergens, injury control, disability prevention, environmental medicine in medical school education, and environmental health in nursing education, practice, and research.

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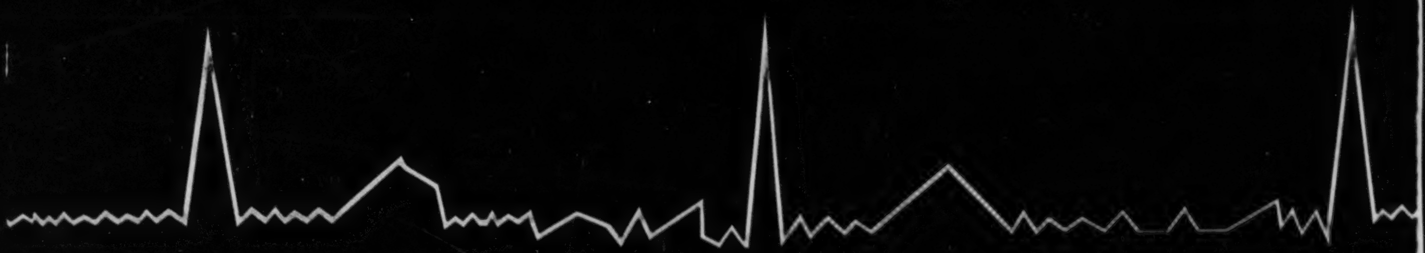

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